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EXACERBACIONES DE ASMA

EN EL SERVICIO DE URGENCIAS DEL HOSPITAL UNIVERSITARIO LA PAZ

Memoria presentada por **Beatriz Pola Bibián** para acceder al grado de Doctor en la Facultad de Medicina de la Universidad Autónoma de Madrid

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PRÓLOGO

La presente tesis se presenta como un compendio de publicaciones científicas de las que la candidata a Doctora es primera autora de dos de ellas y segunda autora de la tercera, de acuerdo con las normas de presentación de tesis doctoral del Programa de Doctorado del Departamento de Medicina de la Facultad de Medicina de la Universidad Autónoma de Madrid.

Esta tesis consta de una introducción general en la que se revisa el estado actual del asma y se explican conceptos básicos, objetivos, la descripción de los pacientes incluidos en cada uno de los estudios, los métodos utilizados, un resumen del resultado de los trabajos, los tres artículos originales, una discusión general y las conclusiones.

Estos trabajos publicados, por un lado inciden, en un aspecto concreto del asma como son las exacerbaciones o reagudizaciones, buscando encontrar ciertas características clínicas o marcadores que puedan ayudar a caracterizar mejor a la población que las sufre con el objetivo de intentar prevenirlas o al menos minimizar su aparición; y por otro lado, se centra en intentar establecer una potencial relación entre los pacientes asmáticos y la presencia de bronquiectasias.

INTRODUCCIÓN

Las enfermedades alérgicas han experimentado un progresivo incremento de su prevalencia a lo largo de las últimas décadas, y esto, junto con la constatación de sus elevados costes tanto en la vertiente económica como en la de la calidad de vida, las convierten en un problema socio-sanitario de primera magnitud.

Una de estas enfermedades es el asma, la cual tiene una importancia creciente por su elevado impacto médico y social y por el enorme coste económico que acarrea y, sin embargo, sigue siendo una enfermedad con muchos aspectos desconocidos. Sus distintos fenotipos no están completamente caracterizados, su patogénesis es extraordinariamente compleja, los factores de riesgo muchas veces son difíciles de determinar, la historia natural es variable y la respuesta al tratamiento, en ocasiones es impredecible. Se trata de una enfermedad que hace de la variabilidad una de sus más importantes señas de identidad, si no la principal.

Por ello, alcanzar y mantener el control del asma se ha convertido hoy en el objetivo del tratamiento. El control traduce el grado en el que las manifestaciones del asma están ausentes o se ven reducidas al máximo por las intervenciones terapéuticas y si se cumplen los objetivos del tratamiento[1]. En función del grado de control, de forma arbitraria, se ha clasificado el asma en: bien controlada, parcialmente controlada y no controlada, si bien, esta clasificación no ha sido validada desde el punto de vista clínico. Aunque el término “control” es amplio, a efectos prácticos incluye las características clínicas de la enfermedad (síntomas y exacerbaciones) y las pruebas de función pulmonar. No obstante, algunos pacientes con asma pueden presentar un buen control de los síntomas y de la función pulmonar y al mismo tiempo tener exacerbaciones frecuentes. Este aspecto es importante porque la estrategia terapéutica para alcanzar

el control debe abordar el control actual, pero también las consecuencias futuras de la enfermedad (riesgo futuro), lo que incluye también la ausencia de exacerbaciones graves y, todo ello, con la menor medicación posible.

El avance de la ciencia nos ha permitido en los últimos años acercarnos más que nunca a la verdadera naturaleza del asma, sin embargo persiste la incertidumbre sobre la importancia de los factores genéticos y ambientales y su interacción, lo cual nos puede conducir a errores en el diagnóstico y en la evaluación clínica de los pacientes y esto traducirse en el ofrecimiento de soluciones inadecuadas al problema médico que se nos plantea. Muchos enfermos continúan sin beneficiarse plenamente de todo lo que se les puede ofrecer hoy día y merecen, por lo tanto, un esfuerzo adicional.

Epidemiología

El asma es la enfermedad respiratoria crónica más prevalente. Afecta aproximadamente a 358 millones de personas en el mundo y está presente en todos los países, independientemente de su grado de desarrollo. Su prevalencia ha aumentado un 12% en los últimos años[2].

En el estudio IBEREPOC, realizado en población española de 40 a 69 años de edad, un 4,9% de la muestra declaró haber sido diagnosticada de asma, con una mayor prevalencia en mujeres[3].

Según la OMS ocurren 250.000 muertes por asma en el mundo cada año. Se estima que el asma causa 1 de cada 250 muertes en el mundo, la mayoría de ellas prevenibles,

debidas a unos cuidados médicos subóptimos y al retraso de la obtención de ayuda durante la exacerbación[4].

En las últimas décadas, las tasas de mortalidad por asma han disminuido en todas las regiones del mundo. En 2015 se registraron 400.000 muertes por asma en el mundo, un descenso del 26,7% en comparación con 1990[2], siendo la mortalidad mayor en zonas menos desarrolladas, lo cual está en relación con la menor disponibilidad de recursos, como acceso a tratamientos. Además, las tasas de mortalidad por asma registradas varían mucho entre los grupos poblacionales, siendo mayores en hombres que en mujeres y ascendiendo de manera exponencial con la edad, como con la mayoría de las causas de muerte.

A pesar de la disminución en las hospitalizaciones y muertes relacionadas con el asma[5], la tasa global de exacerbaciones y los síntomas cotidianos ha aumentado casi un 30% en los últimos 20 años[6] y su tratamiento prácticamente no ha cambiado en los últimos años[7].

De hecho, las exacerbaciones son la principal causa de morbilidad y mortalidad en los pacientes con asma[8], aumentando así el coste anual del tratamiento al triple[9] y suponiendo un riesgo de progresión a enfermedad grave ya que los pacientes con exacerbaciones frecuentes experimentan generalmente una pérdida acelerada de la función pulmonar[10].

Impacto económico

Debido a las elevadas tasas de prevalencia y morbimortalidad, el asma genera un gran consumo de recursos sanitarios, en concreto, en los países desarrollados, del 1 al 2% del gasto sanitario total debe dedicarse a financiar los costes derivados del asma[11].

El coste del asma es considerable tanto en términos de coste directo (coste farmacológico y médico) como en términos de coste indirecto (tiempo de trabajo perdido y muerte prematura). En España se estima que el coste anual del asma es de 1.480 millones de euros, que aumentan con la edad y con la gravedad de la enfermedad; y el coste anual medio del paciente asmático adulto asciende a 1.726 y a 1.533€ desde la perspectiva de la sociedad y del Sistema Nacional de Salud, respectivamente[12].

Las exacerbaciones son uno de los factores que más influye en condicionar una peor calidad de vida en la población asmática, en aumentar el coste de la enfermedad y en el deterioro en el control de la misma. Una sola exacerbación de asma que requiere medicación adicional y posiblemente un tratamiento en Urgencias y/u hospitalización, puede aumentar el coste anual del tratamiento en más de tres veces[13].

Se han intentado diversas estrategias para reducir costes de esta patología, con éxito en algún caso, como la realización de una consulta monográfica de asma grave[14]; o un programa de altas precoces en asma, sin alcanzar la estabilidad del paciente, permitiendo reducir las estancias hospitalarias sin incrementar los reingresos[15]; o la intervención por una enfermera formada en asma, que reduce los ingresos en un 60%, los reingresos en un 54%, la pérdida de días de trabajo y de escolaridad, así como los costes en 6.462 dólares por paciente[16]. Al principio de la década de 1990, en Finlandia

se reconoció el asma como un importante problema de salud pública. A partir de esto se desarrolló un programa multidisciplinar para la asistencia a esta enfermedad. Los resultados obtenidos, con mejoras significativas en todos los indicadores de morbimortalidad, así como lo eficiente de las actividades implementadas, con una disminución del gasto relevante, ponen de manifiesto que el margen de mejora es amplio, y probablemente aplicable en otros países[17].

Definición de asma y exacerbación asmática

El asma es un síndrome complejo con un amplio espectro de presentaciones y manifestaciones clínicas, caracterizado por su gran variabilidad a lo largo del curso de la enfermedad. En su patogenia intervienen diversas células y mediadores de la inflamación, y está condicionada, en parte, por factores genéticos. Cursa con una hiperrespuesta bronquial y una obstrucción variable del flujo aéreo, total o parcialmente reversible, ya sea por la acción medicamentosa o espontáneamente, que produce, entre otros, los síntomas clásicos de tos, disnea, sibilancias y opresión torácica[18].

En todos los subtipos de asma y a todas las edades, independientemente del grado de control y gravedad del paciente, existe el riesgo de deterioro clínico y de la función pulmonar agudo o subagudo. Esta situación se conoce como una exacerbación del asma o ataque de asma.

Existen múltiples definiciones de exacerbación asmática, tradicionalmente se definía como “empeoramiento de los síntomas asmáticos que requiere un cambio en la intensidad del tratamiento para prevenir un deterioro a largo plazo de la enfermedad de base”. En los últimos consensos algunos autores añaden como factor imprescindible

el requerimiento de corticosteroides por vía sistémica, y otros concretan que ésta corticoterapia sistémica debe de durar como mínimo 3 días.

En la actualidad, las definiciones más utilizadas incluyen 3 componentes, todos ellos relacionados con el tratamiento, en lugar de los síntomas: el uso de broncodilatadores de acción corta como los medicamentos de alivio rápido, el uso sistémico de corticosteroides y las visitas al servicio de urgencias u hospitalizaciones.

De manera que, en el momento actual, se podría definir la exacerbación de asma como el empeoramiento de los síntomas de asma y de la función pulmonar, que requieren un aumento en la medicación (incluyendo la terapia sistémica con corticosteroides) y una visita no programada a Urgencias u hospitalización[19].

La intensidad de las exacerbaciones es variable, cursando en ocasiones con síntomas leves e indetectables por el paciente, y en otras con episodios muy graves que ponen en peligro la vida. La gravedad de la exacerbación determina el tratamiento y, por lo tanto, es esencial hacer una evaluación rápida inicial del paciente para determinar si se trata de una exacerbación leve, moderada o grave y establecer el tratamiento preciso de forma precoz[18].

Además según la rapidez de instauración, se pueden dividir en dos subtipos, que deben identificarse por tener causas, patogenia y pronóstico diferentes[18]:

- Exacerbaciones de instauración lenta (normalmente en días o semanas) son más del 80% de las que acuden a Urgencias. Se deben frecuentemente a infecciones respiratorias altas o a un mal control de la enfermedad por incumplimiento terapéutico; el mecanismo fundamental del deterioro es la inflamación; la gravedad inicial es menor y la respuesta al tratamiento es también lenta.

- Exacerbaciones de instauración rápida (en menos de 3 horas) se deben a alérgenos inhalados, fármacos (AINE o β-bloqueantes), alimentos (por alergia alimentaria, especialmente, leche y huevo en la infancia y panalérgenos) o estrés emocional; el mecanismo es la broncoconstricción y, aunque tienen una mayor gravedad inicial (con mayor riesgo de intubación y fallecimiento), la respuesta al tratamiento es más favorable y rápida.

Etiología y factores de riesgo

Las exacerbaciones pueden ocurrir por una sola causa, aunque más comúnmente son el resultado de una combinación de causas, provocando una inflamación compleja.

Las infecciones respiratorias, en especial las de origen vírico, se consideran la principal causa de exacerbación y agravamiento del asma en niños y adultos[20]. La exposición alergénica en pacientes sensibilizados, sobre todo la exposición a aeroalérgenos (pólenes, epitelios de animales, hongos, ácaros), fármacos, alimentos o sustancias presentes en el medio laboral, está cogiendo mayor importancia en los últimos años debido a cambios en el estilo de vida, tales como modificaciones en los hábitos higiénicos o el desarrollo industrial[21].

En los trabajos publicados en los últimos años, el tabaco se asocia de manera concluyente con un mayor nivel de gravedad en el asma y con la falta de control[22]. Otros contaminantes aéreos (dióxido de azufre, dióxido de nitrógeno, ozono o partículas diésel) también tienen un efecto nocivo ya que pueden causar alteraciones en el epitelio bronquial.

Determinadas comorbilidades o condiciones específicas del paciente, se asocian también con un mayor riesgo de exacerbación de asma, tales como la obesidad, el reflujo gastroesofágico, los trastornos psiquiátricos, el síndrome obstructor de apnea de sueño, deficiencia de la vitamina D, raza no blanca, estado socioeconómico bajo, y el sexo femenino[23].

Cualquier situación que condiciona asma mal controlada como haber padecido una exacerbación en el año previo o haber hecho uso de 3 o más ciclos de corticosteroides orales aumenta también el riesgo de exacerbación[5], así como el mal cumplimiento del tratamiento[24]. También el aumento de eosinófilos en esputo y/o en sangre, se han postulado como indicadores de riesgo para padecer una exacerbación de asma[25].

Con respecto a las bronquiectasias, hay cierta controversia, ya que algunos grupos las describen como una comorbilidad asociada al asma[26], pero otros identifican el asma como una de las múltiples causas de aparición de bronquiectasias[27,28,29].

La prevalencia de bronquiectasias en pacientes con asma de cualquier nivel de gravedad es generalmente baja, pero aumenta considerablemente en los pacientes con asma grave (25-51%)[26,30], y se correlaciona con la gravedad del asma[31,32]. La coexistencia de estas dos patologías se ha asociado con un mayor riesgo de exacerbación, hospitalización e insuficiencia respiratoria crónica[33,34].

La incidencia de exacerbaciones en pacientes con asma y bronquiectasias es alta, siendo entre 1,6 y 2,6 veces más probable el presentar una exacerbación que los pacientes que no las tienen[35]. Esto sugiere que la coexistencia de estas dos patologías empeora la evolución de la enfermedad.

Las enfermedades asociadas o comorbilidades contribuyen a un peor control del asma por lo que es imprescindible la investigación y el tratamiento de las mismas, incluso con mayor relevancia en los pacientes con asma grave.

HIPÓTESIS DE INVESTIGACIÓN Y OBJETIVOS

En España, apenas se conocen datos sobre el perfil de los pacientes asmáticos que sufren exacerbaciones. En 2009, se publicó un estudio realizado en Barcelona[36] incluyendo 262 episodios de exacerbación asmática, atendidas en hospitales o en visita domiciliaria, durante 2 meses (octubre y noviembre), siendo la causa más frecuente de las mismas la existencia de una infección de vías respiratorias, posiblemente de origen viral. Previamente, existen datos retrospectivos analizando algunas variables en el área de la calidad asistencial[37] o la epidemiología[38].

Sin embargo, todavía son muchos los aspectos que se desconocen y que podrían servir para prevenir la aparición de exacerbaciones asmáticas. Conocer los factores de riesgo que pueden conducir a una exacerbación, reconocer signos que indiquen su potencial gravedad, e instaurar el tratamiento más adecuado y las medidas de prevención más efectivas, resulta no solamente necesario, sino incluso imprescindible para mejorar el grado de control del asma.

El objetivo primario de la presente tesis es estudiar las características clínicas y demográficas de los pacientes asmáticos de 14 años en adelante, atendidos en el Servicio de Urgencias del Hospital Universitario La Paz, por una exacerbación asmática de cualquier grado de severidad, a lo largo del periodo natural del año 2014.

Como objetivos secundarios se postulan los siguientes:

- Conocer si existen factores predisponentes en esta población para desarrollar una exacerbación asmática.
- Intentar identificar factores desencadenantes de las exacerbaciones asmáticas.

- Determinar si existe un predominio estacional en posible relación con la exposición a alérgenos, particularmente pólenes u otros aeroalérgenos.
- Conocer las tasas de hospitalización, de alteraciones en el recuento de eosinófilos en sangre (eosinofilia) y de derivación a consulta especializada tras el alta de Urgencias.
- Identificar el porcentaje de pacientes asmáticos que tienen recaídas que les obligan a acudir de nuevo al Servicio de Urgencias tras haber sido tratados por una primera exacerbación, y si es posible describir perfiles concretos entre ellos.
- Determinar la prevalencia de bronquiectasias en pacientes con asma moderada-grave, que sufren frecuentes exacerbaciones, con el fin de caracterizarlos mejor tanto epidemiológica como clínicamente.

PACIENTES Y MÉTODOS

La presente tesis se basa en el análisis de dos poblaciones diferentes de pacientes asmáticos que sufren exacerbaciones por lo que aglutina dos proyectos de investigación, ambos aprobados por el Comité Ético de Investigación Clínica (CEIC) del Hospital Universitario La Paz, habiéndose obtenido el permiso para el uso de datos confidenciales.

En primer lugar, se llevó a cabo un estudio epidemiológico, abierto, observacional retrospectivo (no intervencionista) en el que se incluyeron todos los pacientes mayores de 14 años, que desde el 1 de enero de 2014 al 31 de diciembre de 2014, fueron atendidos en el Servicio de Urgencias del Hospital Universitario La Paz, con clínica sugerente de exacerbación asmática.

El Hospital La Paz es un hospital terciario, y es centro de referencia para una población de 500.000 personas, en el norte de Madrid. El número total de visitas al Servicio de Urgencias fue de 211.031 en el año 2014[39].

Se comenzó la recogida de datos a partir de enero de 2015. Se realizó una búsqueda en la base de datos del Servicio de Urgencias del hospital, siguiendo los códigos de asma determinados en la 9ª revisión de la Clasificación Internacional y Estadística de Enfermedades y Problemas Relacionados con la Salud (ICD-9-CM) (493; 493.0; 493.1; 493.2; 493.8; 493.9) y realizando posteriormente una búsqueda complementaria buscando otros posibles diagnósticos no codificados, tales como asma bronquial, broncoespasmo, hipersensibilidad bronquial, bronquitis asmática, bronquitis espástica, sibilantes, estado asmático, crisis asmática, ataque asmático agudo o grave y agudización del asma. Se completaron las hojas de recogida de datos a partir de los informes de alta del Servicio de Urgencias.

Se recogieron 84 variables, agrupadas en los siguientes 5 apartados:

- Características del paciente: epidemiológicas, comorbilidades (HTA, DM, EPOC, etc., incluyendo el diagnóstico de asma y su grado de control) y tratamientos regulares (AINES, betabloqueantes, IECAs, estatinas, corticosteroides inhalados, etc.).
- Evaluación de la exacerbación de asma: factores desencadenantes, síntomas (tos, ruidos torácicos, rinoconjuntivitis, etc.), pruebas complementarias (en especial el número de eosinófilos en sangre) y nivel de gravedad de la exacerbación (de acuerdo con los criterios de consenso de la ATS/ERS para ensayos clínicos)[40].
- Tratamiento administrado en Urgencias: oxígeno, broncodilatadores, corticosteroides, antibióticos, etc.
- Respuesta del paciente al tratamiento y la actitud llevada a cabo: alta, observación, ingreso hospitalario, ingreso en UCI o muerte.
- Seguimiento: derivación a una consulta especializada al alta (Alergología, Neumología, etc.).

Cada episodio de exacerbación se definió como un evento. Cuando el paciente acudía nuevamente a Urgencias en un plazo inferior a 15 días desde la crisis inicial, se consideró una recaída, mientras que si lo hacía en un periodo posterior, contabilizaba como un nuevo episodio.

En el primer capítulo de esta tesis se realizó un estudio descriptivo en el que se analizaron las características clínicas y epidemiológicas de los pacientes que habían sufrido una exacerbación de asma en el periodo de inclusión. También se describen los

desencadenantes más frecuentes de las exacerbaciones, los predictores de hospitalización y el potencial papel de la eosinofilia periférica.

En el segundo capítulo el objetivo fue identificar la frecuencia de recaídas que ocurrían tras una exacerbación de asma tratada en el servicio de Urgencias, las causas y los potenciales factores predictores de las mismas.

En segundo lugar, se realizó un estudio epidemiológico también abierto, observacional retrospectivo sobre el que versa el tercer capítulo de esta tesis. En él se analizaron las historias clínicas de 264 pacientes derivados a la Consulta de Asma Grave del Hospital La Paz, entre los años 2010 y 2013, con sospecha de asma grave o mal controlada.

El asma grave se definió de acuerdo con el consenso de la Sociedad Respiratoria Europea (ERS) y el grupo de trabajo de la Sociedad Torácica Americana (ATS) sobre asma grave[41].

El diagnóstico se confirmó objetivamente en todos los pacientes mediante una prueba de respuesta broncodilatadora o una prueba de provocación bronquial con metacolina positiva. Una vez que se confirmó el diagnóstico, se realizaron los estudios adicionales establecidos para todos los pacientes con asma grave.

De las historias clínicas revisadas, se seleccionaron para el análisis 184 pacientes, a los que se les había realizado una tomografía computarizada torácica de alta resolución, y se realizó un estudio comparativo de los resultados obtenidos en los pacientes con bronquiectasias frente a los que no las tenían.

Se recogieron las siguientes variables:

- Datos demográficos

- Gravedad y control del asma (GINA), tratamientos, número de exacerbaciones y hospitalizaciones
- Valores espirométricos
- Enfermedades asociadas o concomitantes: atopia, rinitis alérgica, dermatitis atópica, rinosinusitis crónica, reflujo gastroesofágico, hipersensibilidad a AINEs
- Sensibilización frente a aeroalérgenos comunes (determinada por test cutáneos y niveles de IgE específica)
- Análisis de sangre (específicamente niveles de eosinófilos, proteína catiónica eosinofílica y de anticuerpos anticitoplasma de neutrófilo)
- Tomografía computarizada torácica de alta resolución (bronquiectasias)
- Otras pruebas complementarias en función de situación de cada paciente: TC de senos paranasales, test del sudor, pHmetría, etc.

RESULTADOS

En el primer trabajo incluido en esta tesis la población de estudio comprendió 831 pacientes (888 eventos de exacerbación). La mayoría de los episodios de exacerbación asmática ocurrieron en enero y mayo. El desencadenante más frecuente fue la infección respiratoria, presente en 523 eventos. En un 34,21% de los casos, el recuento de eosinófilos fue ≥260/mm3 (≥400/mm3 en 20,7%), lo que se asoció significativamente con el asma alérgica (P <0,0001). Los factores de riesgo de hospitalización fueron: edad avanzada (OR, 1,58, IC 95%, 1,46-1,71), la ausencia de un diagnóstico previo de asma (OR, 1,40, IC 95%, 1,06-1,86), el asma mal controlada (OR, 1,78; 95 % CI, 1,10-2,88), la infección respiratoria (OR, 2,65; IC 95%, 1,95-3,62) y la exacerbación grave con mayor necesidad de tratamiento. La tasa de hospitalización fue significativamente menor en pacientes con ≥400 eosinófilos/mm3 (p <0,001).

En el segundo trabajo se analizaron 52 pacientes (de los 831 previos), que sufrieron una recaída después de haber sido atendidos en el Servicio de Urgencias, haciendo un total de 66 episodios. La probabilidad promedio de recaída fue de 6 ± 0,8%. La frecuencia de episodios fue mayor en mayo y noviembre. Veinticuatro pacientes tenían ≥260 eosinófilos/mm3 en sangre, incluidos 17 que tenían ≥ 400 eosinófilos/mm3. Solo el 15% de los pacientes fueron remitidos a un especialista en asma en el momento del alta. Los factores relacionados con una mayor probabilidad de recaída fueron: haber tenido visitas múltiples al Servicio de Urgencias en un año, asma no controlada, sibilancias en la auscultación pulmonar, eosinofilia periférica ≥400/mm3 y haber sido dado de alta en la primera visita al Servicio de Urgencias (p <0,01 para todos).

En el tercer trabajo se identificaron bronquiectasias en 86 pacientes (47% de los pacientes asmáticos a los que se les había hecho una TC torácica de alta resolución). Estos pacientes tenían hipersensibilidad a antiinflamatorios no esteroideos (OR 2,24, IC 95% 1,00-5,03) y enfermedad por reflujo gastroesofágico (OR 1,89, IC 95% 1,05-3,41) con mayor frecuencia que los sujetos sin bronquiectasias, pero menor frecuencia de dermatitis atópica (OR 0,188, IC 95% 0,04-0,88). Los sujetos con bronquiectasias tuvieron una tasa mayor de hospitalización por exacerbaciones de asma (OR 2,09, IC 95% 1,08-4,05) y niveles más altos de eosinófilos en sangre (464 vs 338, p <0,005) que los sujetos sin bronquiectasias.

CAPÍTULOS

CAPÍTULO 1

Asthma Exacerbations in a Tertiary Hospital: Clinical Features, Triggers, and Risk Factors for Hospitalization

(Exacerbaciones de asma en hospital terciario: características clínicas, desencadenantes y factores de riesgo para hospitalización)

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ABSTRACT

Background: The risk factors for asthma exacerbations are not fully understood. The aim of this study was to determine the epidemiological and clinical characteristics of patients who experience asthma exacerbations. We also assessed potential triggers of exacerbations and possible predictors of hospitalization.

Methods: A retrospective, noninterventional cohort study was conducted in adult patients who attended the emergency department of a tertiary hospital with an asthma exacerbation during 2014.

Results: The study population comprised 831 patients (888 events). Most episodes occurred in January and May. Respiratory infection was the trigger in 523 events. In 34.21% of cases, the eosinophil count was ≥260/mm3 (≥400/mm3 in 20.7%), which was significantly associated with allergic asthma (P <.0001). The risk factors for hospitalization were older age (OR, 1.58; 95%CI, 1.46-1.71), no previous diagnosis of asthma (OR, 1.40; 95%CI, 1.06-1.86), poorly controlled asthma (OR, 1.78; 95%CI, 1.10-2.88), respiratory infection (OR, 2.65; 95%CI, 1.95-3.62), and severe exacerbation with more treatment requirements. The rate of hospitalization was significantly lower in patients with ≥400 eosinophils/mm3 (P <.001).

Conclusion: Older age, absence of a previous asthma diagnosis, uncontrolled disease, and concomitant chronic obstructive pulmonary disease are frequent among patients presenting at the emergency department with asthma exacerbations. Various features were associated with a higher risk of admission. Blood eosinophilia should be considered a marker of asthma, but not a predictor of hospitalization.

Key words: Asthma. Exacerbation. Risk of hospital admission. Eosinophilia

INTRODUCTION

Most patients with asthma remain symptomatic despite maintenance treatment and experience exacerbations, which are indicative of poor asthma control [1]. An asthma exacerbation is defined as worsening of asthma symptoms and lung function that requires an increase in medication (including systemic corticosteroid therapy), a visit to the emergency department, or hospitalization [2]. Although some countries have seen a decline in asthma-related hospitalizations and deaths [3], the global burden of exacerbations and day-to-day symptoms has increased by almost 30% in the past 20 years [4]. In fact, exacerbations are the main cause of morbidity and mortality in patients with asthma [5], thus increasing the annual cost of treatment 3-fold [6]. Patients who have frequent exacerbations usually experience an accelerated loss of lung function [7].

Asthma exacerbations are commonly triggered by upper respiratory tract infections and/or exposure to environmental allergens and, less frequently, by other factors [8]. The specific features and conditions associated with an increased risk of exacerbations in adults include obesity, smoking, severe sinus conditions, allergy, gastroesophageal reflux (GER), repeated respiratory infections, psychiatric disorders, obstructive sleep apnea syndrome, vitamin D deficiency, nonwhite race, low socioeconomic status, and female sex [9]. Indicators of poor asthma control (eg, an exacerbation in the previous year or ≥3 cycles of oral corticosteroids, poor treatment adherence [10], and eosinophilia in sputum [11] or blood [12]) are considered risk factors for exacerbation.

Knowing which risk factors could lead to an exacerbation, recognizing indicators of potential severity, and establishing the most appropriate treatment and more effective

preventive measures are not only necessary, but could prove indispensable for improving control of asthma. The profile of asthma exacerbations in Spain has been assessed. In 2009, the results of a study of 262 episodes of asthma exacerbation treated in a hospital emergency department (ED) and home care services in Barcelona [13] revealed that the most frequent etiology was possible viral infection of the respiratory tract, although the observation period was limited to October and November. Retrospective studies have been published on quality of care [14] and epidemiology [15]. Many relevant issues associated with exacerbations remain unresolved, and more information could help to prevent onset.

The present study was designed to assess the epidemiological and clinical characteristics, potential triggering factors, and possible predictors of hospitalization in patients (with or without a prior diagnosis of asthma) who had experienced at least 1 asthma exacerbation and were treated in the ED of a tertiary hospital in Spain.

METHODS

We conducted a retrospective and observational (noninterventional) cohort study using data collected from medical records and charts at the ED of La Paz University Hospital, Madrid, Spain. This hospital is the tertiary referral center for a population of 500 000 in northern Madrid. The total number of ED visits was 211 031 in 2014 [16]. The study was approved by the local ethics committee, and permission was obtained from the hospital for the use of confidential data.

A specific search was performed following any of the International Statistical Classification of Diseases and Related Health Problems 9th Revision (ICD-9-CM) codes for asthma (493; 493.0; 493.1; 493.2; 493.8; and 493.9) [17], and a supplementary search was later performed following other possible and noncoded diagnoses, namely, bronchial asthma, asthmatic bronchitis, asthmatic crisis, acute asthma attack, and asthma exacerbation. Events in which chronic obstructive pulmonary disease (COPD) or COPD exacerbation was mentioned as a possible cause for the ED visit were excluded. An isolated diagnosis of pneumonia was also excluded. All patients aged >14 years who attended the ED with one of the aforementioned “labels” suggestive of an asthma exacerbation from January 1 to December 31, 2014 were enrolled. Data were collected by the same 4 investigators during the inclusion period. Each episode was defined as an event. After discharge from the ED or hospital and a period of 7 days of stability after resolution of an exacerbation [18,19], cases in which the same patient visited the ED less than 15 days after the previous event were classified as relapses, while visits after this 15-day period were considered new events.

For each event, 84 variables were identified for data collection and grouped under the following 5 headings: (1) patient characteristics, namely, epidemiology and comorbid conditions (including asthma diagnosis and previous level of control according to then current consensus criteria of the 2009 Spanish guideline on asthma management [GEMA]) [21], and regular treatments; (2) evaluation of the asthma exacerbation (trigger factors if they were explicitly recorded in the chart [ICD-9-CM codes 465 and 466 for respiratory infections, 477 for allergic rhinitis, 372 or 995 for allergy, and 935.8 for nonsteroidal anti-inflammatory drugs]) [17], clinical features, such as cough, wheezing, and fever), and severity of the exacerbation (defined by GEMA 2009) [20], laboratory tests (especially eosinophil count, with eosinophilia defined as ≥260/mm3 in blood) [21]; (3) treatment administered at the ED; (4) patients' response to treatment, and subsequent outcome (discharge, observation, hospital admission, intensive care admission, or death); and (5) referral to an asthma specialist (allergist or pulmonologist) at discharge. As elevated blood eosinophil counts have been proposed as a risk factor for asthma exacerbations, we also considered a cutoff of 400/mm3, as previously reported [12].

Statistical Analysis

Quantitative data are expressed as mean (SD), maximum, and minimum. Discrete variables are presented as a frequency distribution, percentages, and, when necessary, 95% confidence intervals. The Pearson chi-square test or Fisher's exact test were used as appropriate for a univariate exploratory analysis of discrete variables. Correlated data were analyzed using a generalized linear mixed model (GLMM) with the restricted maximum pseudolikelihood method. With respect to the first objective, the "probability

of the event" (for each event separately: asthma event, admission, and relapse), a random intercept, and an unstructured covariance matrix were added to the GLMM with a binomial distribution and logit link function to test the need for a random effect. If a random effect was not necessary, logistic regression was used to estimate the probability of the event. Specific epidemiological and clinical variables were then added into the model, and their relationships with the binary outcome were estimated and expressed as the odds ratio (OR). The Mann-Whitney test was used to assess the role of eosinophil level (<260/mm3) and patient age. The relationship between age and the month of the event was estimated using Spearman correlations. All tests were 2-tailed, and significance was set at P<.05. An exploratory univariate analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp), while GLMM analysis was carried out using SAS Enterprise Guide 5.1 (SAS Institute Inc). The procedures used were "proc glimmix" and "proc logistic".

RESULTS

The study population comprised 831 patients (563 women), who experienced 888 episodes; 54 patients had >1 episode. Mean age was 57.3 years (range, 14-102 years). Data on patient characteristics and comorbidities are shown in Table 1. When information on variables such as obesity, GER, or confirmed nasal polyps could not be collected from a sufficient number of patients, it was not included in the final analysis. The average likelihood of relapse was 6% and that of hospitalization 32% (Table 2).

In this population, 45.7% of patients (n=380) had no previous recorded diagnosis of asthma. Among those already diagnosed with asthma (n=451), 81 were not receiving regular treatment, 108 (23.94%) used only a short-acting b-agonist (SABA) as needed, and 255 (more than half of the known asthmatic population) were on regular treatment with inhaled corticosteroids with or without long-acting ß-agonists. A total of 102 patients (12.27%) had experienced at least 1 exacerbation requiring emergency care in the previous year. Only 15 patients had ever been admitted to the intensive care unit.

A blood eosinophil count was obtained from 681 patients. Overall, 233 patients (34.21% of those tested) had an eosinophil count ≥260/mm3, whereas 141 (20.7% of the tested population) had >400/mm3. Eosinophilia was weakly associated with younger age and weakly but significantly associated with a diagnosis of respiratory allergy (P<.0001). The OR for this association increased by 1.16 (95%CI, 1.11.22) for every additional 100 cells/mm3.

The distribution of the total 888 events per month is shown in Figure 1. The frequency of episodes was highest in January and May (142 [16%] and 158 [17.8%], respectively) and lowest in July and August. However, April and November were the months with the

highest rates of hospitalization (43.4% and 38.3%, respectively). The suspected etiologies of the exacerbations and their clinical characteristics are reported in Table 3. Respiratory infection was the most common trigger for exacerbation (523 episodes [58.9%]), followed by direct exposure to aeroallergens (in 70 episodes [7.9%]). The triggering agents or factors were not identified in 29% of episodes.

As for severity, 319 of the 888 exacerbations (35%) were considered moderate-to-severe, with a risk of imminent respiratory arrest in 5 cases. The most common symptoms were dyspnea (90%) and cough (78%), mostly without expectoration (54%). Ten patients arrived with an altered level of consciousness. Physical examination revealed wheezing in 77% of cases and absent breath sounds in only 25 patients. Baseline oxygen saturation <92% was observed in 31% of patients. Overall, 51% of the episodes required systemic corticosteroids, and 25% were treated with antibiotics. After treatment, approximately 68% of patients were discharged (8.3% after staying in an observation bay), and 259 patients (285 events [32.1%]) were admitted (6 to the intensive care unit). No fatal events due to asthma attacks were registered.

Associations between the variables of interest and hospitalization are shown in Table 4. In general, the variables associated with a higher risk of admission were older age (Figure 2), absence of a previous diagnosis of asthma or uncontrolled disease, suspected respiratory infection, severe crisis, and increased need for ED treatment. However, only 25.5% of patients with a blood eosinophil count >400/mm3 required hospitalization, compared with 44.2% of those with <400/mm3 (P<.001).

DISCUSSION

The incidence of asthma exacerbations according to reallife surveys is much higher than in clinical trial settings [4]. Moreover, exacerbations affect patients with poorly controlled asthma irrespective of severity, even in those treated with inhaled corticosteroids [23]. Loss of asthma control usually leads to unscheduled clinical visits; in one study, 70% of uncontrolled asthmatics had an unscheduled visit to a physician, 36% had an ED visit, and 14% had been hospitalized in the previous year [24]. Indeed, experiencing an asthma exacerbation in the previous year is the strongest predictor of future exacerbations in adults [25]. In the population we studied, a large number of asthmatics were receiving SABA monotherapy. Despite the major role of inflammation in asthma and even 15 years after the AIRE study, in which more patients had used rescue medication (63%) than inhaled corticosteroids (23%) in the previous 4 weeks [26], we still find that many patients diagnosed with asthma are not on regular maintenance treatment. This might be a consequence of an overestimation of asthma control that does not match symptom severity. However, the number of patients who had visited the ED during the preceding year was lower in our sample than in other published observational studies [23], and, interestingly, did not significantly predict a new exacerbation during the period analyzed.

A potential limitation of the present study was the lack of data for all the outcomes, which was a consequence of the retrospective design. Therefore, a prospective cohort is warranted to assess the actual influence of previous exacerbation. One of the major strengths, however, is the inclusion of patients seen in the same hospital by the same ED medical team throughout the year, which decreases the risk of bias, even as a result

of seasonal patterns. Our sample is representative of real-life practice in our geographic area and indicates that a substantial number of asthmatic patients might not be correctly diagnosed and may be receiving substandard care or even going untreated. It is remarkable that 45% of the patients who experienced an asthma exacerbation in this study had no previous diagnosis of asthma or that this disease had not been adequately entered into the medical record in the ED. We believe that the retrospective character of the study may have influenced data collection, especially since we only considered data recorded in the charts, as is the case in real-world practice, and therefore tried to avoid any interpretation bias by the investigators. In the ASMAB II study [13], only 31% of the patients attending the ED used inhaled corticosteroids regularly. Dominguez-Ortega et al [27] analyzed 83 bronchospasm episodes managed in the ED during a storm in spring: 21% of the patients had no previous recorded diagnosis of asthma, 93% had no regular medical visits, and 61.45% did not receive any treatment for asthma. Serrano-Pariente et al [28] defined 3 different phenotypes of patients who had experienced a near-fatal asthma attack. In cluster 3 in particular, which was characterized by insufficient anti-inflammatory treatment and frequent sensitization to Alternaria alternata and soybean, only 4% of patients had undergone periodic medical monitoring of their asthma, only 30% had received inhaled corticosteroids, and none had followed a written action plan for asthma during the attack [28]. Misdiagnosis of asthma has been reported in stable disease, leading to inappropriate treatment and suboptimal patient outcomes [29], and could affect up to 26% of frequent exacerbators (requiring ≥2 ED visits or hospitalization) [30]. It is also remarkable that more than 40% of patients were not referred to a specialist on discharge despite having required urgent attention, thus

missing an opportunity for collaboration between ED physicians, allergists, and pulmonologists.

Although it has been reported that women [31] and current smokers [32] are at higher risk of asthma exacerbations, surprisingly, we did not find a high associated prevalence in either group in our study. In contrast, older age and previously uncontrolled disease were more prevalent in both groups. We did not analyze these outcomes independently, since older patients are usually at risk for poorer future asthma control [33]. We also found that, in our population, age was associated with a higher rate of hospitalization. Moreover, in the sample studied, 13.7% of patients had been previously diagnosed with COPD. The prevalence of asthma and COPD overlap syndrome among adults with COPD or asthma ranges from 13% to 30%, and patients with the syndrome usually have severe disease, with increased rates of exacerbation and hospitalization [34]. Accordingly, we found a frequent association between asthma and comorbid COPD in the population we studied. These results are in agreement with those of a recent Italian multicenter observational study conducted in patients older than 65 years with documented physician-diagnosed asthma. The authors highlighted the negative impact of COPD on asthma control [35]. We also found frequent associations with comorbidities that are also more prevalent among the elderly, such as arterial hypertension, diabetes, and psychiatric disorders. The perception of dyspnea has been reported to decrease with worsening asthma, advancing age, and depression status. Patients with major depression had 3.4-fold higher odds of asthma than those with minimal or no depressive symptoms [36]. Other comorbidities are being explored, with GER, atherosclerosis, hypertension, ischemic heart disease, lipid disorders, and neoplastic disease possibly playing a role, as all have been shown to significantly worsen the degree of asthma

control [37]. However, further research is needed to assess whether these comorbidities might influence the risk of exacerbation.

Although no biomarkers accurately predict asthma exacerbations, an elevated eosinophil count in sputum or blood has been associated with a higher risk of asthma exacerbation and hospitalization [12]. Eosinophilic asthma is a common phenotype, and the blood eosinophil count may be useful, as it is easy to assess in clinical practice [38]. However, the issue of whether the blood eosinophil count can confirm an eosinophilic phenotype and the optimal cutoff point for an increased risk of exacerbation remain open to debate. Based on previous recommendations [22], we selected a cutoff of 260/mm3. In addition, 300/mm3 has been reported to be a potential biomarker associated with a successful response to omalizumab [39]. Furthermore, in the PREDUNA study [40] (a retrospective cohort study that examined the relationship between blood eosinophil count at baseline and asthma exacerbations in the following 12 months), a cutoff of ≥400/mm3 was strongly associated with future uncontrolled asthma (exacerbations and excessive SABA use). However, we found no association between blood eosinophil count and presence of exacerbation. This finding is in agreement with the results of Tran et al [41], who did not find a clear association in a 10-year survey of adults, although they did find a clearer trend toward increased asthma attacks after an additional adjustment for levels of exhaled FeNO and treatment for asthma in the previous 3 months [41]. Moreover, neutrophilic inflammation has been consistently observed in acute asthma associated with viral respiratory tract infections [42], in contrast to noninfective causes of asthma, which are characterized by increased IL-5 and eosinophil activation, thus suggesting differential patterns of inflammation depending on the etiology of the exacerbation.

It is interesting that eosinophil levels in children were significantly higher in those who reported more asthma attacks (median blood eosinophil count, 300 cells/mm3), suggesting that higher blood eosinophil counts might play a different role in children with asthma than in adults with the disease. A higher rate of allergic asthma could influence these results. In allergic asthma, inflammation is clearly associated with the presence of eosinophils in the airway and characteristic TH2 cytokine expression [43]. As expected, we found allergic asthma to be significantly associated with a higher blood eosinophil cutoff point. Nevertheless, we found a significant inverse association between eosinophil count and risk of admission. This finding differs from those of the pilot study by Hasegawa et al [44], who found that, of 80 patients hospitalized for asthma exacerbation, 32 patients (40%) had blood eosinophilia (300/mm3). However, the study was limited by the inclusion of patients with severe acute asthma in the analytic cohort population, which may suggest that their study population was in poorer health than the overall population of patients hospitalized for asthma exacerbation. In our population, the frequency of infection as a cause of exacerbation was exceedingly high, and this may have influenced eosinophil counts [45]. Moreover, the low frequency of hospitalizations due to acute allergic exposure in this population might also have influenced the results, thus decreasing the impact of eosinophilia in the whole population.

In conclusion, asthma exacerbations generate a significant burden for patients with asthma and for the health care system. In this large, population-based study of asthma exacerbations treated at a tertiary hospital over a 1-year period, we found that several factors were relatively common in asthmatics experiencing exacerbation and could be related to the risk of hospitalization. Older age, absence of a previous asthma diagnosis,

uncontrolled disease, and concomitant COPD were frequent among patients with exacerbated asthma. These factors were also associated with a higher risk of admission, as were respiratory infections, severity of the exacerbation, and need for intensive treatment in the ED. Blood eosinophil counts should be considered a specific marker of the asthma phenotype, but not as a predictor of hospital admission. Further studies are warranted to better elucidate the role of each specific variable in predicting asthma exacerbations and risk of hospitalization.

Table 1. Demographic and clinical features of the study population. n=831

	Nº (%)
Gender	563 female (67.7) /268 male (32.3)
Smokers	150 (18.1)
Ex-smokers	102 (12.3)
Previous diagnosis of Asthma	451 (54.3)
Previous diagnosis of respiratory allergy	117 (14.1)
Previous diagnosis of COPD	114 (13.7)
Previous diagnosis of psychiatric disorders	166 (20)
Previous diagnosis of drug allergies	135 (16.2)
Previous diagnosis of high blood pressure	296 (35.6)
Previous diagnosis of Diabetes mellitus	116 (14)
Previous diagnosis of dyslipidemia	131 (15.8)
Regular treatment with Statins	150 (18)
Regular treatment with ACE inhibitors	138 (16.6)
Regular treatment with Betablockers	72 (8.7)
Regular treatment with NSAIDs	27 (3.3)

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug.

Table 2. Average probability of hospitalization, more than one event and relapse in the studied population estimated by a Generalized Linear Mixed Model.

Effect	Estimate	Standard Error	p	Mean	Standard Error Mean
Admission	-0.7496	0.0721	<.0001	0.3209	0.01569
≥1 event	-0.0420	0.1052	<.0001	0.1149	0.01070
Relapse	-2.7372	0.1404	<.0001	0.06081	0.008020

Table 3. Clinical characteristics of the exacerbations. (n=888).

Severity	%
Mild	60
Moderate/Severe	35
Imminent respiratory arrest	0.5
Suspected Triggers	
Respiratory infection	59
Respiratory allergy	8
Physical exercise	0.8
Drug intake	0.6
Psychological factors	0.6
Food allergy	0.1
Others and unknown	28
Symptoms	
Dyspnoea	90.5
Cough	78
Expectoration	46
Wheezing	43
Low level consciousness	1.1
Chest tightness	15
Nasal symptoms	13
Ocular symptoms	4
Physical examination	
Auscultation: normal	19.5
Auscultation: wheezing	78
Auscultation: abolished sounds	2.5
Tachycardia > 99 lpm	33.5
Tachypnea>19 rpm	26.8
High temperature (>37.7ºC)	3.6
Basal oxygen saturation <92%	31

Table 4. Relationship between hospitalization and the outcomes analyzed

OUTCOME	OR	CI 95% OR
Older age	1.58	1.46-1.71
Male gender	0.981	0.724-1.328
No previous diagnosis of asthma	1.403	1.056-1.863
Uncontrolled asthma	1.786	1.105-2.879
Mild exacerbation (VS moderate/severe)	0.091	0.065-0.128
Ex-smokers VS smokers	1.746	1.073-2.843
Previous diagnosis of DM	3.247	2.205-4.781
Previous diagnosis of DL	2.020	1.401-2.912
Previous diagnosis of respiratory allergy	0.324	0.194-0.539
Previous diagnosis of drug allergies	2.130	1.489-3.048
Previous diagnosis of High blood pressure	3.778	2.805-5.089
Respiratory infection as a trigger	2.655	1.948-3.618
Respiratory allergy as a trigger	0.159	0.068-0.369
Blood eosinophilia (>260/mm^3)	0.459	0.327-0.644
Arterial blood gases in the ED	8.314	5.783-11.954
Treatment with Oxygen	7.082	5.142-9.753
Treatment with short acting inhaled B-2 agonists	1.825	1.290-2.581
Treatment with corticosteroids	2.374	1.741-3.238
Treatment with inhaled ipratropium bromide	1.935	1.372-2.729
Treatment with antibiotics	10.379	7.286-14.787

Figure 1. Monthly distribution of exacerbations.

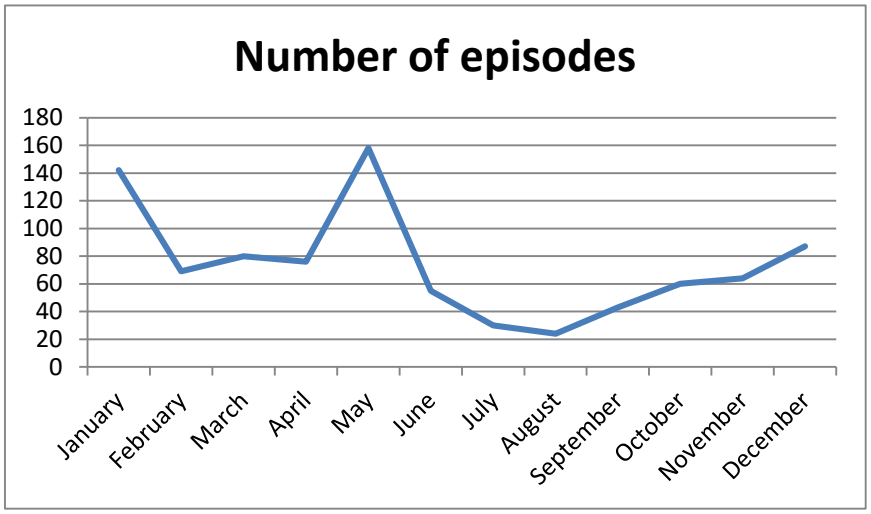
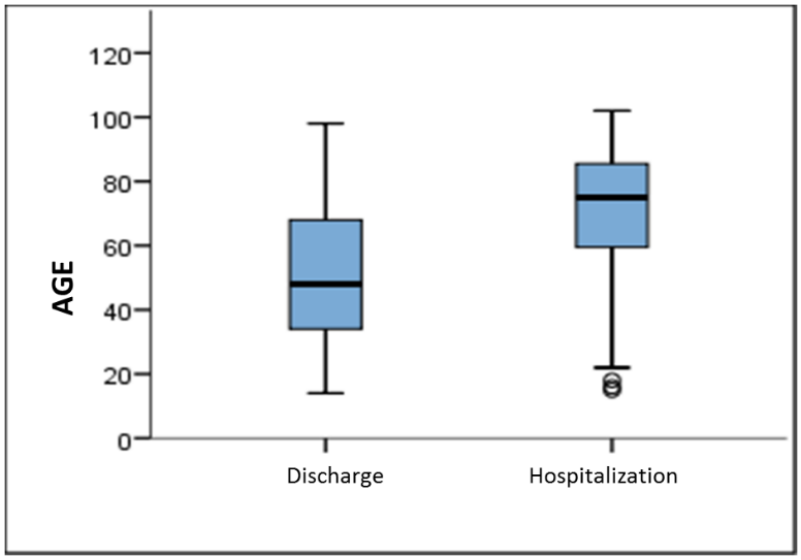


Figure 2. Relation between age and hospitalization



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CAPÍTULO 2

Predictors of asthma relapse in patients attending the Emergency Department

(Predictores de recaídas de exacerbaciones de asma en pacientes atendidos en el Servicio de Urgencias)

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ABSTRACT

Background: Patients with asthma exacerbations and frequent relapses requiring admission to the Emergency Department (ED) often have more severe disease, worse quality of life and higher use of health care resources.

Objective: The aim of this study was to identify potential predictors of relapse after an asthma exacerbation treated in the ED.

Methods: A retrospective, non-interventional cohort study was conducted in adult patients who attended the Emergency Department of a tertiary hospital for an asthma exacerbation in 2014. We analyzed the sub-population who experienced at least one relapse (return the ED less than 15 days after the previous event).

Results: Fifty-two out of 831 patients suffered 66 relapses after being attended at the ED (mean age 58.5±23.4 year-old). The average probability of relapse was 6±0.8%. The frequency of episodes was higher in May and November. Twenty-four patients had ≥260 blood eosinophils/mm3, including 17 who had ≥ 400 eosinophils/mm3. Only 15% of the patients were referred to an asthma specialist at discharge. Factors related to a higher probability of relapse were: having multiple visits to ED in one year, uncontrolled asthma, wheezing in the pulmonary auscultation, peripheral eosinophilia ≥400/mm3 and being discharged in the first visit at the ED ($p<0.01$ for all).

Conclusions: In this population, patients who have multiple ED visits in one year, those with uncontrolled asthma, wheezing, ≥400 blood eosinophils/mm3 or who had been discharged at the first ED visit are at higher risk of relapse.

Keywords: asthma, exacerbation, morbidity, emergency department, discharge, relapse, eosinophilia, follow-up, specialist, predictors of relapse.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, with variable airflow obstruction and episodic exacerbations [1]. This disease represents one of the principal causes of Emergency Department (ED) attendance [2]. Indeed, the ED is increasingly recognized as a major setting of asthma care, and asthma has been identified as an independent risk factor for frequent ED use [3]. Acute exacerbations occur in asthma across the whole spectrum of severity, in spite of maintenance treatment, and they constitute the major cause of morbidity and mortality [4], raising the annual cost of treatment threefold [5] and accelerating loss of lung function in these patients [6].

Despite the fact that most patients with acute asthma attended in EDs are safely discharged home [7, 8, 9], a remarkable percentage of patients are at risk for relapse. In fact, previous studies have described relapse proportions around 12% in the first 2 weeks after discharge [10, 11]. Moreover, patients with frequent relapses requiring admissions to ED often have more severe disease and use a disproportionately high share of health care and resources [12, 13]. As a matter of fact, reducing relapses after treatment for acute asthma exacerbations represents a notable improvement in the patients' quality of life, a reduced strain on crowded EDs, and an opportunity to decrease direct healthcare costs [10].

Relentless airway inflammation, poorly-resolving infection and persistent bronchial hyperreactivity may all play a role in the pathophysiology of asthma relapse [12], and correspondingly, there is evidence demonstrating the effectiveness of systemic corticosteroids in reducing relapses among adults [14, 15, 16]. Further studies suggest

that inhaled corticosteroids at ED discharge could also play an important role on relapse reduction [17].

Up to now, there is little published evidence to characterize this population. Identifying predictors of relapse, modifiable risk factors of relapse and indicators of severity could help design focused interventions for the prevention of subsequent relapses [18]. The present study was designed to characterize the population at a higher risk of relapse and to gain some insight in the related risk factors.

METHODS

We retrospectively analyzed the data from a sub-population of a large observational, retrospective, cohort of 831 patients who had experienced at least one asthma exacerbation and who were treated in the ED [9]. The data was collected from medical records or charts at the ED of La Paz University Hospital, a tertiary referral center in Madrid (Spain). The institutional Ethics Committee approved the study.

A specific search was performed for all of the International Statistical Classification of Diseases and Related Health Problems 9th Revision (ICD-9-CM) codes for asthma [19], and a supplementary search was later performed following other possible and no-codified diagnoses: bronchial asthma, asthmatic bronchitis, asthmatic crisis, acute asthmatic attack and asthma exacerbation. We excluded every event in which COPD or a COPD exacerbation was mentioned as a possible cause for the ED visit. The study included patients aged ≥14 years who attended the ED with one of the aforementioned "labels" suggestive of an asthma exacerbation, from January 1st to December 31st, 2014. Each episode was defined as an event and a relapse was defined as a return to the ED less than 15 days after the previous event [11].

A number of 84 variables were identified for data collection, grouped under the following five headings: 1) Patient characteristics: epidemiology, comorbid conditions (including recorded asthma diagnosis and previous level of control according to GEMA 2009) [20] and regular asthma treatment; 2) Evaluation of asthma exacerbation: triggering factors (according to ICD-9-CM codes) [21]; clinical features, such as cough, wheezing, fever, etc.; severity of the exacerbation (defined by GEMA 2009) [18]; and

laboratory tests, with particular attention to eosinophilia; 3) Treatment administered at the ED; 4) Patients' response to treatment and subsequent outcome (discharge, observation, hospital admission, intensive care admission, or death) and finally; 5) Referral to an asthma specialist (allergist or pulmonologist) at discharge.

Eosinophilia was defined as ≥260 eosinophils per microliter (mm3), in blood [21]. As elevated blood eosinophil counts have been proposed as a risk factor for asthma exacerbations, we also considered a cutoff of 400 eosinophils/mm3 as previously reported [22]. When it was not possible to collect enough registered data from a sufficient number of patients for any variable (obesity or nasal polyps), the outcome was not finally analyzed for the study.

Statistical analysis

Quantitative data are expressed as mean ± standard deviation (SD), maximum and minimum. Discrete variables were presented by frequency distribution, percentages and when necessary, the 95% confidence intervals were calculated. For the univariate exploratory study of discrete variables, the Pearson Chi-square test or Fisher's exact test were used. For quantitative variables, the Mann-Whitney test was performed. To estimate the average probability of relapse a Generalized Linear Mixed Model (GLMM) with the Restricted Maximum Pseudo-Likelihood Method (RMPL) was used. Random intercept, unstructured covariance matrix, binomial distribution and logit link function were defined by the model. All bilateral tests and statistically significant results when $p < 0.05$ were considered. The exploratory univariate analysis was performed using the 20th version of statistical software SPSS for Windows, and the analysis based on the

Generalized Mixed Model was carried out with SAS Enterprise Guide 5.1 software (Cary NC, SAS Institute Inc., USA), in particular the procedure used was "*proc glimmix"*.

RESULTS

In 2014, the total number of ED visits was of 211,031 [23]. Fifty-two out of 831 patients (mean age 58.5 ± 23.4 year-old [17 to 95]) suffered 66 relapses after being attended at the ED with an asthma exacerbation in 2014. Table 1 shows patient characteristics and comorbidities, in comparison with the total population, with no significant differences between them. The average probability of relapse for patients was 6±0.8%.

Of these, 23 patients (44.2%) had no recorded diagnosis of asthma in the charts. Among the 29 patients with a recorded diagnosis of asthma, 8 did not follow any regular treatment. Only 7 used short-acting beta-agonist (SABA) as needed, and 11 were treated with inhaled corticosteroids (ICS) alone or in combination with long-acting beta-agonists (LABA). Moreover, 12 of these 29 patients (41.3%) had suffered from at least one exacerbation in the previous year that required emergency care, and only one patient had been ever admitted in an intensive care unit (ICU).

The frequency of episodes was higher in May (22.2%) and November (13%), whereas it was much lower in July and August (Figure 1). On the other hand, the months with highest probability of relapse were May and June, together accounting for 30.3% of the relapses.

The clinical characteristics of the exacerbations are reported in Table 2, showing differences with total population, not statistically significant. The suspected trigger for the exacerbation was a respiratory infection in more than half the episodes (37 episodes; 56%) and direct exposure to aeroallergens in 5 episodes (7.6%). In 22 episodes (33%), the triggering agent was not reflected in the charts. An eosinophil blood count

was performed in all the patients. Twenty-four patients (46.2%) had ≥260 eosinophils/mm3, 17 of which had ≥ 400 eosinophils/mm3.

Overall, 45.2% of the episodes were treated with systemic corticosteroids, 54.8% with ICS, 69.4% with a SABA, and 16.1% with antibiotics.

In comparison with total population, in which 51% of the episodes were treated with systemic corticosteroids, and 25% with antibiotics, it is clear that relapse population was less treated.

After treatment, the patients were discharged in 55 episodes (8 of them with previous stay in the observation area) and hospitalized in 11 episodes but no patients required admission to the ICU; no fatal events were registered. Among those who were discharged, a combination of ICS-LABA was prescribed in 44% of the episodes, antibiotics in 37% and oral corticosteroids in 29% (similar percentages in total population). Follow-up with a respirologist or allergologist was only recommended in 15% of the cases.

Compared to the total study group (831 patients), factors with a significantly higher probability of relapse were having multiple ED visits in the year, uncontrolled asthma, wheezing on pulmonary auscultation, blood eosinophilia ≥400/mm3 (Figure 2) and being discharged in the first ED visit (Table 3).

DISCUSSION

Relapse is a frequent complication of asthma exacerbations. However, in this study, the average probability of relapse was around 6%, lower than reported in other studies. Relapse rates of 17% in the first 14 days [24] and up to 45% at 8 weeks after discharge have been described [25]. *Hasegawa et al [26]* concluded that approximately 15% of patients had readmissions within 30 days after a hospital discharge, and that the readmission rate was highest in the first week after discharge. These differences in rates might be due to variations in the inclusion criteria used in some of these studies, such as only including patients that needed hospitalization and therefore with more severe exacerbations and an increased likelihood of relapse. In addition, some of the studies did not report the treatment administered in the ED nor previous patients' treatment. Some other factors could have influenced our results. On one hand, perhaps our patients were receiving a more intense maintenance treatment since more than a half had been well controlled prior to their first exacerbation. On the other hand, our ED could be prescribing systemic corticosteroids frequently than others.

Finally, it is worth considering that the location of our hospital, far from the city centre, so some patients, especially those with mild to moderate exacerbations, may have gone to a neighbourhood Health Centre to receive prompt medical treatment instead of returning to the hospital.

One potential weakness of this study was the unavailability of data for all the outcomes, due to its retrospective design. It is remarkable that only 55.8% of the patients who experienced a relapse had a previous diagnosis of asthma or, alternatively, that the asthma diagnosis had not been adequately registered in the medical record at the ED.

Thus, we believe our sample is representative of real-life practice in our area. This could indicate that a substantial number of asthmatic patients might not be correctly diagnosed and could be receiving suboptimal care. We believe that the retrospective nature of this study may have influenced data collection, especially since we only considered the data that had been recorded in the charts, according to real-world conditions and trying to avoid any interpretation bias by the investigators. However, among the well-identified asthmatic group, the proportion of uncontrolled asthma patients seems to be high, and previous studies show that uncontrolled asthma results in a higher risk of future asthma exacerbations [27, 28, 29]. In fact, a history of an asthma exacerbation in the previous year is recognized as the strongest predictor of future exacerbations in adults [30]. However, our study, while 41.3% of the asthmatics had suffered at least one exacerbation in the previous year, less than the 40% of them were on maintenance treatment for asthma. Moreover, frequent ED users are more likely to have several markers of severe asthma, such as previous hospital admissions and the current use of inhaled corticosteroids [31]. Concordantly, in our study, having multiple events (several visits to the ED in a year) and having an uncontrolled asthma were related to a higher probability of relapse. According to the 2007 NAEPP guidelines, multiple asthma-related ED visits within 1 year are indicative of uncontrolled asthma and are therefore, theoretically preventable with high-quality health care, patient education and optimal asthma management [32].

Comorbidities are often linked to poor control and severity in asthma [33]. A high percentage of our population had comorbidities such as cardiovascular diseases, active smoking, hay fever and psychiatric disorders. Our results are similar to those reported by *Denlinger et al [34]* who concluded that patients with exacerbation-prone asthma

showed a higher proportion of hypertension and diabetes mellitus but was not related to age or sex. Asthma and COPD overlap (ACO) has a prevalence of 13 to 30% in patients with asthma [35], and usually presents with a more severe disease, increased rates of exacerbation and hospitalization [36]. Even in non-smoker asthmatics with persistent airway limitation, the number of patients with at least one asthma-related exacerbation or hospitalization and/or emergency interventions during the last year was higher [37]. Accordingly, we found a significant association between asthma and comorbid COPD in this population. The coexistence of one or more comorbidities could hinder optimal asthma control.

Concordantly with previous studies, the suspected trigger in more than half of the exacerbations was respiratory infection [38]. However, the specific data in our study indicates the months with the highest probability of relapse were May and June, suggesting an important role for pollen allergy-related attacks in our area [39].

Related to treatment, it is concerning that only 45.2% of the asthma episodes were treated with systemic steroids so we have identified what appears to be undertreatment of asthma exacerbations.

An elevated eosinophil count in sputum and blood has been found to be associated with a higher risk of asthma exacerbation and hospitalization [9]. The PREDUNA study [40], a retrospective cohort study that examined the relationship between blood eosinophil count at baseline and asthma exacerbations in the following 12 months, suggested that a blood eosinophil cut-off of ≥400/mm3 was strongly associated with future uncontrolled asthma (defined as exacerbations and excessive SABA use). In this study,

32% of the patients who suffered a relapse had a blood eosinophil count ≥400/mm3. In fact, it was significantly associated with a higher probability of relapse but not hospitalization. *Denlinguer et al [30]* also reported that adults with exacerbation-prone asthma have higher blood eosinophils levels than other asthma phenotypes. Unfortunately, other inflammatory biomarker measurements such as FENO [41] are not routinely performed at the ED in our hospital.

It was previously reported that follow-up visits are effective in reducing early relapses in patients who have been treated for asthma in the ED [42, 43] and that asthma treatment interventions by specialists outside the ED were associated with a reduced number of ED visits and hospitalizations [44]. In this study we show that only 15% of the patients were referred to an asthma specialist, which could make our population more susceptible to relapse. With a similar approach, *Hasegawa et al [32]* reported that specialists had attended only 15% of patients with ≥6 ED visits in the previous year. Only a very small subset of frequent users of the ED for asthma exacerbations received outpatient management by asthma specialists and were recommended long-term control therapy [32]. It is important to encourage ED clinicians to recommend specialized follow-up after a relapse. The integration of the specialist into the system would help prevent asthma exacerbations and select patients who should receive regular asthma care and close follow-up, further reducing asthma morbidity [45].

To conclude, our data provides some insights on the characteristics associated with relapses in patients with asthma exacerbations. This is particularly relevant for practicing clinicians involved in the management of patients with asthma during and

after an exacerbation, looking to prevent relapses. Patients who have multiple events, uncontrolled asthma, ≥ 400 blood eosinophils/mm3 or who were discharged at the first ED visit are at higher risk of relapse. Therefore, we believe that our findings can assist physicians to better understand, identify and manage this specific patient population.

Table 1. Baseline demographic and clinical characteristics of the population.

	Relapse population (n=52)	Total population (n=831)
Gender	38 female (73.1%) / 14 male (26.9%)	563 female (67.7%) /268 male (32.3%)
Smokers, n (%)	6 (11.5%)	150 (18.1%)
Ex-smokers, n (%)	9 (17.3%)	102 (12.3%)
Previous diagnosis of Asthma, n (%)	29 (55.8%)	451 (54.3%)
Respiratory allergy, n (%)	7 (13.5%)	117 (14.1%)
COPD, n (%)	7 (13.5%)	114 (13.7%)
Psychiatric disorders, n (%)	12 (23.1%)	166 (20%)
Drug allergies, n (%)	9 (17.3%)	135 (16.2%)
High blood pressure, n (%)	21 (40.4%)	296 (35.6%)
Diabetes mellitus, n (%)	9 (17.3%)	116 (14%)
Dyslipidemia, n (%)	10 (19.2%)	131 (15.8%)
Treatment with Statins, n (%)	8 (15.4%)	150 (18%)
Treatment with ACE inhibitors, n (%)	10 (19.2%)	138 (16.6%)
Treatment with Betablockers, n (%)	6 (11.5%)	72 (8.7%)
Treatment with NSAIDs, n (%)	3 (5.8%)	27 (3.3%)

*COPD: Chronic Obstructive Pulmonary Disease.

*ACE inhibitors: Angiotensin Converting Enzyme inhibitors.

*NSAIDs: Nonsteroidal Anti-inflammatory Drugs.

Table 2. Comparison of clinical characteristics of the exacerbations between relapse population and total population.

	Relapse population (n=52)	Total population (n=831)
Number of exacerbation episodes	66	888
Severity		
Mild	46 (70.3%)	532 (60%)
Moderate/Severe	20 (29.7%)	310 (35%)
Imminent respiratory arrest	0 (0%)	4 (0.5%)
Suspected Triggers		
Respiratory infection	37 (56%)	532 (60%)
Aeroallergen exposure	5 (7.6%)	79 (9%)
Physical exercise	0 (0%)	7 (0.8%)
Drug intake	1 (1.5%)	5 (0.6%)
Psychological factors	1 (1.5%)	5 (0.6%)
Food allergy	0 (0%)	1 (0.1%)
Others and unknown	22 (33%)	248 (28%)
Symptoms		
Dyspnoea	60 (90.9%)	803 (90.5%)
Cough	52 (78.8%)	692 (78%)
Expectoration	25 (37.9%)	408 (46%)
Wheezing	36 (54.5%)	381 (43%)
Low level of consciousness	0 (0%)	9 (1.1%)
Chest tightness	4 (6.1%)	133 (15%)
Nasal symptoms	10 (15.2%)	115 (13%)
Ocular symptoms	5 (7.6%)	35.5 (4%)
Physical examination		
Auscultation: normal	15 (22.7%)	173 (19.5%)

Auscultation: wheezing	51 (77.3%)	692 (78%)
Auscultation: abolished sounds	0 (0%)	22 (2.5%)
High temperature (>37.7ºC)	0 (0%)	32 (3.6%)
Basal oxygen saturation <92%	14 (21%)	275 (31%)

Table 3. Factors associated to increased probability of asthma exacerbation of relapse in the total population (p<0.01).

Risk factors	**Percentage of relapse**
Multiple events	22.2%
Uncontrolled asthma	20.9%
Wheezing	9.5%
Peripheral eosinophilia >400/mm3	12.1%
Discharged in first visit	9.2%

Figure 1**.** Monthly distribution of exacerbations in patients with relapses.

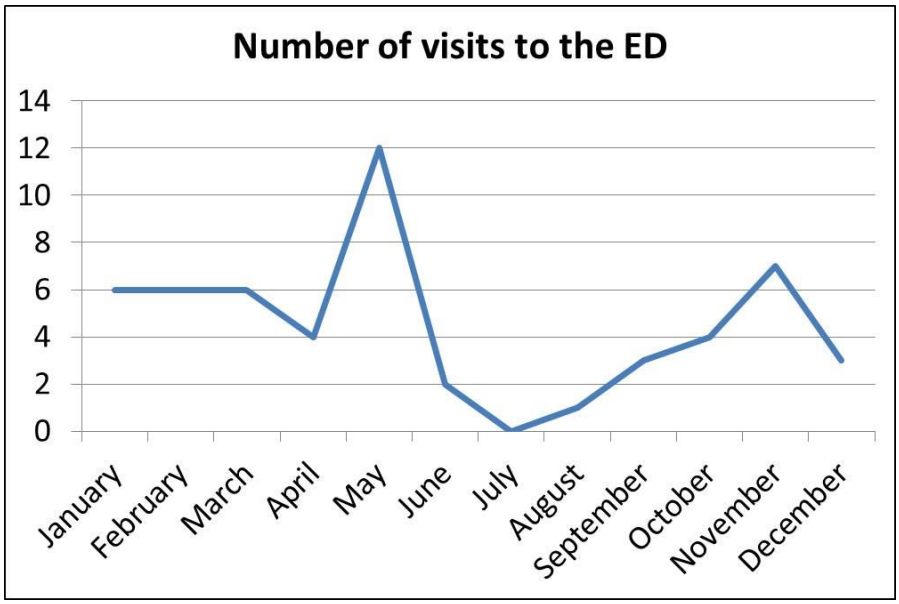
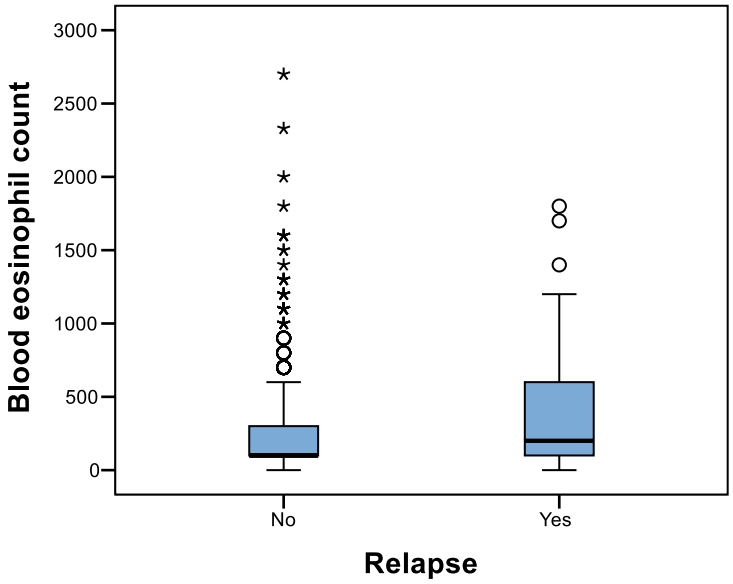


Figure 2. This figure represents the relationship between relapses and blood eosinophil count. Patients with relapses have a significant increased number of blood eosinophils.

The boxes and vertical lines represent the range in which most values are included. The circles and stars represent outliers, which are atypical and extreme values, outside of superior limits.



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CAPÍTULO 3

Bronchiectasis in severe asthma:

clinical features and outcomes

(Bronquiectasias en asma grave: características y resultados clínicos)

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ABSTRACT

Background: Bronchiectasis is increasingly being identified in patients with severe asthma and could contribute to disease severity.

Objective: To determine the prevalence of bronchiectasis in a population of patients with severe asthma and to better characterize the clinical features of these patients and their outcomes.

Methods: We retrospectively reviewed the medical files of 184 subjects with confirmed severe asthma who had undergone high-resolution thoracic computed tomography and compared the characteristics and outcomes of subjects with and without bronchiectasis.

Results: Bronchiectasis was identified in 86 patients (47%). These patients had concomitant hypersensitivity to nonsteroidal anti-inflammatory drugs (odds ratio [OR] 2.24, 95% confidence interval [CI] 1.00-5.03) and gastroesophageal reflux disease (OR 1.89, 95% CI 1.05-3.41) more frequently than subjects without bronchiectasis, but had less atopic dermatitis (OR 0.188, 95% CI 0.04-0.88). Subjects with bronchiectasis were more frequently hospitalized for asthma exacerbations (OR 2.09, 95% CI 1.08-4.05) and had higher blood eosinophil levels (464 vs 338; P = .005) than subjects without bronchiectasis.

Conclusion: Our study suggests that in subjects with severe asthma, the presence of bronchiectasis is associated with more frequent hospitalizations, concomitant gastroesophageal reflux disease, hypersensitivity to nonsteroidal anti-inflammatory drugs, and higher blood eosinophil counts. Bronchiectasis could represent an additional phenotypic feature of severe eosinophilic asthma.

INTRODUCTION

Despite having a prevalence of 5-10% of all asthma cases, severe asthma disproportionately contributes to asthma-related healthcare costs [1,2]. The investigation and treatment of comorbidities is of major importance in patients with severe asthma, as they contribute to poor disease control.

Bronchiectasis are defined radiologically as a focal or diffuse irreversible dilation of the airways and results from loss of elastin, muscle, cartilage, with variable fibrosis of bronchial walls and peribronchial changes [3]. Some groups have described bronchiectasis as a comorbidity associated to asthma [4] while others have identified asthma as being one of many etiologies of bronchiectasis [5, 6,7]. The presence of bronchiectasis has been reported in 17.5-80% of asthma cases [8, 9,10] and asthma severity and bronchiectasis have both been linked to atopy [11] and sensitization to fungi such as Alternaria, Cladosporium and Aspergillus [12, 13].

In this study, we aimed to retrospectively determine the prevalence of bronchiectasis in our population of patients with severe asthma and to describe the characteristics and outcomes of these patients In terms of exacerbation rates and hospitalizations. Furthermore, as sensitization to fungi is associated to poor asthma control and disease complications, we hypothesized that the prevalence of fungal sensitization in patients with bronchiectasis would be higher than in patients without bronchiectasis.

METHODS

Subjects

We retrospectively collected data from patients referred for evaluation of severe or uncontrolled asthma to the Severe Asthma Clinic of Hospital La Paz, between 2010 and 2013. Severe asthma was defined according to the European Respiratory Society and American Thoracic Society Taskforce on Severe Asthma [1]; asthma required Global Initiative for Asthma step 4 or 5 treatment (ie, high-dose inhaled corticosteroid with a long-acting β-agonist or leukotriene modifier or theophylline) or systemic corticosteroid use at least 50% of the previous year to maintain control or remained "uncontrolled" despite this treatment.

The diagnosis was objectively confirmed in all patients by means of bronchodilator response testing or a positive methacholine bronchial provocation test reaction [14]. Once the diagnosis was confirmed, additional standard investigations were performed in all patients with severe asthma. Sensitization to common aeroallergens including local pollens (Cupressus arizonica, Platanus acerifolia, Olea europaea, Gramineae mix, Artemisia vulgaris), dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farinae, Lepidoglyphus destructor), cockroach, fungi (Aspergillus fumigatus, Alternaria alternata, Cladosporium herbarum), cat and dog dander were determined by skin prick testing (SPT) and specific IgE levels. SPT results were considered as positive when eliciting a wheal diameter ≥ 3mm, using negative (saline) and positive (histamine 10mg/mL) controls for interpretation [15]. Measurement of total serum IgE levels and specific IgE levels for aeroallergens and fungi (A. fumigatus, A. alternata, C. herbarum, C. albicans) were performed in all patients, using a commercial ImmunoCAP kit

(ThermoFisher Scientific, Uppsala, Sweden). Atopy was defined as the presence of at least one positive SPT or specific serum IgE. Basic hematology, serum levels of eosinophilic cationic protein (ECP) and serum antineutrophilic cytoplasmic antibody (ANCA) levels were also performed in all patients, as well as High Resolution Computed Tomodensitography (HRCT) of the thorax. Additional investigations such as sinus CT scan, sweat test, pHmetry were performed as needed on a per-patient basis. Alternative diagnoses such as but not limited to smoking-related chronic obstructive pulmonary disease (COPD), allergic bronchopulmonary mycosis (ABPM), and cystic fibrosis (CF) were investigated and ruled out based on clinical suspicion and investigation results. We included patients referred for uncontrolled or severe confirmed asthma who completed the above investigations. The institutional ethics commitee of the hospital approved the study and the use of confidential data.

Bronchiectasis on HRCT

Standard criteria for bronchiectasis diagnosis on thoracic HRCT complied with the Spanish Society of Pneumology and Thoracic Surgery recommendations and were the identification of a bronchuswithaninternaldiameterlargerthanthatof itsaccompanying vessel or the absence of bronchus tapering in the periphery of the lungs [16]. Most HRCTs were performed in the context of the asthma investigation, unless results were available from an HRCT performed within the past 6 months.

Statistical analysis

Demographic, clinical, and functional information was collected from the medical history and electronic files of all included patients. Statistical analysis was performed with IBM SPSS Statistics 25 (IBM Corp, Armonk, New York). Values were expressed as

mean ± SD.Continuous variables were compared using the Student t test, and the $\chi 2$ or Fisher exact test was used to compare categorical variables. All P values are taken from 2-tailed tests and values less than .05 were considered statistically significant. Logical regression analyses were performed using 95% confidence intervals (CIs).

RESULTS

A total of 264 patients were referred for evaluation of severe asthma. After the exclusion of 80 subjects who did not have thoracic HRCT results or interpretation, data from 184 patients were analyzed. Demographic, clinical, and functional data according to the presence or absence of bronchiectasis are presented in Table 1. More than 90% of patients were on Global Initiative for Asthma treatment steps 4 and 5. Of the 184 patients, 86 (47%) had bronchiectasis. These subjects were on average older tan those without bronchiectasis. Patients with bronchiectasis had a concomitant diagnosis of intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs; 22% vs 11%; P=.046, odds ratio [OR] 2.24, 95% CI 1.00– 5.03) and gastroesophageal reflux disease (GERD; 62% vs 46%; P=.033, OR 1.89, 95% CI 1.05–3.41) more frequently than those without bronchiectasis. Atopic dermatitis was less frequently documented in subjects with bronchiectasis (2% vs 11%; P=.019, OR 0.188, 95% CI 0.04–0.88).

There was no difference in common aeroallergen and fungal sensitization, because 22% of subjects in each group were sensitized to any of 4 fungi (A fumigatus, A alternata, C herbarum, C albicans). Subjects with bronchiectasis had significantly higher blood eosinophil levels (464 vs 338; P=.005) and higher serum eosinophil cationic protein levels (58 vs 43; P=.003) than subjects without bronchiectasis but had comparable IgE levels (P 0.65). There was no significant difference in maintenance treatment between groups. In the year before evaluation in our service, 83 subjects (97%) with bronchiectasis and 88 subjects (90%) without bronchiectasis presented at least 1 asthma exacerbation, with similar exacerbation averages in the 2 groups (3.45 vs 3.39; P=.09, OR 3.14, 95% CI 0.84–11.82). More patients with bronchiectasis were hospitalized for

an asthma exacerbation in the year before the consultation in our service compared with patients without bronchiectasis (35% vs 20%; P=.028, OR 2.09, 95% CI 1.08–4.05). The association remained significant when adjusted (Table 2) for the presence of GERD and intolerance to NSAIDS in multiple logistical regression analysis (OR 2.02, 95% CI 1.03–3.98). When specifically looking at subjects on maintenance oral corticosteroids, there was no difference in exacerbations, hospitalizations, blood eosinophil counts, or eosinophilic cationic protein between subjects with and without bronchiectasis.

DISCUSSION

Bronchiectasis is a frequent finding that affected half the subjects with severe asthma in our population.Patients with coexistent severe asthma and bronchiectasis are twice as likely to be hospitalized for asthma exacerbations as patients with severe asthma alone, and the coexistence of the 2 conditions is associated with hypersensitivity to NSAIDS, GERD, and higher blood eosinophil counts.

At least 1 abnormality was detected by thorax HRCT in up to 85% of subjects with asthma; the most commonly reported were trapped air, bronchial wall thickening, and bronchial dilation [17,18]. The prevalence of bronchiectasis in patients with any severity of asthma is generally low, increases considerably in patients with severe asthma (25%–51%) [4,17] and is generally correlated to asthma severity [16,19] as in the present study.The coexistence of these 2 pathologies has been associated with an increased risk of exacerbation, hospitalization, and chronic respiratory failure [20,21]. One group reported that half their patients with coexistent asthma and bronchiectasis had been hospitalized for an asthma exacerbation at least once in their lifetime compared with 17.6% of patients with asthma alone [19]. Our study exclusively collected data on events that occurred the year before the patients'evaluation in our unit. Although exacerbation rates were similar, 35% of subjects with bronchiectasis had been hospitalized at least once compared with 20% of subjects without bronchiectasis (P=.028).

The reported prevalence of asthma in subjects with bronchiectasis ranges from 2.7% to 40% [19,22]. The 2017 US Bronchiectasis Research Registry [23] reported a clinical diagnosis of asthma in 29% of patients, but fewer than 5% of patients had confirmed asthma. In fact, in recent cohort studies, asthma was identified as the etiology of

bronchiectasis in only 3% to 5.4% of cases [6,24] and the British Thoracic Society non–cystic fibrosis bronchiectasis guidelines [7] suggest the consideration of asthma as the etiology of bronchiectasis in the absence of other causes. Asthma was the etiology of bronchiectasis in 5.4% of 2,047 patients in a Spanish Registry Study and was correlated to poorer lung function but less chronic bronchial infection [25]. The incidence of exacerbations in patients with asthma and bronchiectasis is high, with patients being 1.6 to 2.6 times as likely to present an exacerbation as patients without bronchiectasis [26]. This suggests that the coexistence of these 2 pathologies worsens outcomes, as in the present study.

Our results associated the presence of bronchiectasis with the coexistence of hypersensitivity to NSAIDS and GERD, 2 important comorbidities of asthma. The prevalence of aspirin-exacerbated respiratory disease in severe asthma is 15% [27] and is strongly associated with exacerbations [28] but it has not been associated with bronchiectasis in the current literature. In contrast, the reported prevalence of GERD in asthma is 35%–82% [29] (and 26%–75%4,22 in bronchiectasis), and it has been associated with poor disease control and increased risk of exacerbation for the 2 pathologies [30,31]. However, there are limited data on the effects of treating GERD in patients with asthma [32] or bronchiectasis [33] because most studies have significant limitations and report divergent results.

Although early studies documented a relation among asthma, bronchiectasis, and atopy [34,35] many others did not [19,21] even when specifically looking at subjects with severe asthma as in the present study. Likewise, some studies have documented an association between bronchiectasis and fungi-sensitized asthma [36]. However,

compared with our study, patients with allergic bronchopulmonary micosis are always not systematically excluded from analyses of bronchiectasis and fungal sensitization in asthma [37]. Because the criteria used for allergic bronchopulmonary mycosis vary greatly, these patients also might be mislabeled as having severe asthma with fungal sensitization. This could explain why we did not observe an association between fungal sensitization and bronchiectasis in our patients. In contrast, the lower incidence of atopic dermatitis in subjects with bronchiectasis, in the context of comparable levels of total serum IgE levels, could be hypothetically explained by factors such as fungal colonization [38]. In atopic dermatitis, a T-helper cell type 2 response is developed against common allergens, which in turn promotes IgE secretion by plasma cells. However, in patients with asthma and bronchiectasis, in the absence of other criteria of allergic bronchopulmonary aspergillosis, the increased secretion of IgE could be driven by other factors such as fungal colonization and infection [39] which have previously been associated with increased total serum IgE levels.

It is difficult to determine whether the severity of asthma in subjects with coexistent bronchiectasis is due to the presence of bronchiectasis or whether the presence of bronchiectasis is a manifestation of asthma severity. The higher levels of blood eosinophils and eosinophil cationic protein we observed in patients with coexistent bronchiectasis (464vs338, P=.005; and 58vs43, P=.003, respectively) seem to suggest the latter. Induced sputum was not systematically performed in our population, but there is a strong correlation between sputum and blood eosinophil levels in patients with asthma [40]. Our findings suggest that the presence of bronchiectasis could be another criterion to identify patients with severe eosinophilic asthma (SEA), thus identifying a subset of patients among those with SEA [41].

Macrolides have been proved to lower exacerbation rates in subjects with asthma and subjects with non–cystic fibrosis bronchiectasis [42,43] often at the cost of increased antimicrobial resistance. In the recent AMAZES [44] trial, regular treatment with azithromycin decreased the rate of severe exacerbations requiring treatment with systemic corticosteroids or hospitalization (incidence rate ratio 0.59, 95% CI 0.42–0.83) in subjects with moderate to severe asthma. Although there were only 3 patients on longterm azithromycin treatment in our study, the addition of azithromycin to current treatment regimens could prove beneficial in this population. The large number of patients and the systematic investigations performed in all patients evaluated in the multidisciplinary severe asthma unit are important strengths of the present study. The limitations are mainly related to its retrospective design. The bronchiectasis documented by HRCT was not classified or scored according to severity and was included in the analysis, whether or not it was clinically significant. However, had only clinically significant bronchiectasis been considered, it would likely strengthen the associations found in our study. Although recall bias could underestimate the exacerbation and hospitalization rates, this would be expected to affect the 2 groups.

Bronchiectasis was identified in half our population of subjects with severe asthma and is independently associated with an increased risk of hospitalization. Our study suggests an association among bronchiectasis, concomitant GERD, and hypersensitivity to NSAIDs, a finding that deserves further exploration. These patients also present higher serum eosinophil counts than comparable subjects without bronchiectasis and could represent a phenotype within SEA. The extent of the immunopathologic roles of the eosinophil in SEA has yet to be fully understood, and prospective studies on routine

HRCT and active treatment of bronchiectasis in subjects with severe asthma are needed to help guide management in this population.

Table 1. Demographic characteristics

Patient characteristics n (%)	**Asthma with bronchiectasis 86 (47%)**	**Asthma without bronchiectasis 98 (53%)**	**p (sig < 0.05)**
Age, avg (SD)	56 (16.49)	48 (13.12)	**0.003**
Gender, n (%)	67 (78%)	78 (78%)	0.954
Smoker, n (%)	45 (52%)	46 (47%)	0.466
GINA treatment step, n (%)			
Step 3	5 (6%)	12 (12%)	0.133
Step 4	59 (69%)	55 (56%)	0.082
Step 5	22 (26%)	31 (32%)	0.366
Oral antileukotriene, n (%)	50 (58%)	56 (57%)	0.678
Inhaled anticholinergic, n (%)	46 (53%)	45 (46%)	0.305
Oral azithromycin, n (%)	3 (3%)	0 (0%)	0.082
Oral corticosteroids, n (%)	25 (29%)	28 (29%)	0.941
Omalizumab, n (%)	14 (16%)	12 (12%)	0.433
FEV_1%, avg (SD)	76% (23.45)	82% (23.99)	0.972
FEV_1/FVC %, avg (SD)	66% (13.40)	71% (15.48)	0.584
Atopy, n (%)	51 (59%)	61 (62%)	0.683
Allergic rhinitis, n (%)	46 (53%)	27 (28%)	0.230
Chronic rhinosinusitis, n (%)	31 (36%)	27 (28%)	0.216
Atopic dermatitis, n (%)	2 (2%)	11 (11%)	**0.019**
NSAIDS intolerance, n (%)	19 (22%)	11 (11%)	**0.046**
Gastroesophageal reflux disease, n (%)	53 (62%)	45 (46%)	**0.033**
Total serum IgE, avg (SD)	383 (600)	356 (821)	0.65
Blood eosinophils/mm3, avg	464 (445)	338 (260)	**0.005**
Eosinophil Cationic Protein, avg (SD)	58 (47)	43 (35)	**0.003**
Sensitizations (skin prick)			
Cupressus arizonica	20 (23%)	25 (26%)	0.723

Platanus acerifolia	8 (9%)	18 (18%)	0.078
Olea europaea	22 (26%)	27 (28%)	0.763
Gramineae	28 (33%)	43 (44%)	0.116
Artemisia vulgaris	6 (7%)	8 (8%)	0.762
Chenopodium album	13 (15%)	20 (20%)	0.351
D. pteronyssinus	5 (6%)	14 (14%)	0.060
D. farinae	8 (9%)	15 (15%)	0.219
Lepidoglyphus destructor	10 (12%)	9 (9%)	0.587
Cockroach	3 (3%)	1 (1%)	0.252
Alternaria alternata	2 (2%)	6 (6%)	0.208
Aspergillus fumigatus	7 (8%)	8 (8%)	0.995
Cladosporium herbarum	1 (1%)	3 (3%)	0.378
Cat dander	13 (15%)	28 (23%)	0.154
Dog dander	23 (23%)	26 (27%)	0.350
Sensitizations (serum IgE)			
Candida albicans	7 (8%)	13 (13%)	0.268
Aspergillus fumigatus	15 (17%)	11 (11%)	0.229
Sensitization (prick or IgE) to ≥ 1 fungus	19 (22%)	22 (22%)	0.954
Had ≥ 1 exacerbation/yr, n (%)	83 (97%)	88 (90%)	0.076
Exacerbations/yr, avg (SD)	3.45 (2.21)	3.39 (2.73)	0.090
Had ≥ 1 hospitalisation/yr, n (%)	30 (35%)	20 (20%)	**0.028**
Hospitalizations/yr, avg (SD)	0.56 (0.94)	0.31 (0.71)	**0.004**

Table 2. Predictors of bronchiectasis in subjects with severe asthma

	Odds ratio	**95% CI**
Smoking status	1.241	0.695-2.216
Atopy	0.884	0.488-1.600
Allergic rhinitis	0.698	0.387-1.256
Rhinosinusitis	1.482	0.794-2.768
Atopic dermatitis	0.188	**0.041-0.875**
Intolerance to NSAIDS	2.243	**1.000-5.032**
GERD	1.892	**1.050-3.408**

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DISCUSIÓN GENERAL

El asma es una enfermedad heterogénea, un síndrome complejo caracterizado por su gran variabilidad a lo largo del curso de la enfermedad, en la que existe el riesgo de un deterioro agudo o subagudo de la función pulmonar.

La incidencia de exacerbaciones de asma parece ser más alta en la vida real de lo que aparece en la bibliografía[6], y afectan a pacientes con un mal control del asma, independientemente de la gravedad de la enfermedad, incluso a aquellos tratados con corticosteroides inhalados, lo cual conlleva un mayor número de visitas a Urgencias y de hospitalizaciones, suponiendo una importante carga para el sistema sanitario. De hecho, la historia de una exacerbación de asma en el año previo es el predictor más importante de futuras exacerbaciones en adultos[42].

En los últimos años, diversos estudios han demostrado que las exacerbaciones de asma se asocian con un mayor descenso de la función pulmonar en comparación con individuos que no las presentan y que el impacto es mayor a medida que aumenta el número de exacerbaciones en un determinado periodo de tiempo, independientemente de la edad de los pacientes y del nivel de gravedad del asma[43], por lo que la prevención de las mismas debería de ser uno de los objetivos principales del tratamiento de la enfermedad.

Todavía existe un porcentaje alto de asmáticos que no realizan un tratamiento de mantenimiento, y que únicamente están tratados con SABA (broncodilatadores de acción corta) en monoterapia, a pesar del importante papel de la inflamación en el asma y 18 años después del estudio AIRE en el que la mayoría de los pacientes habían usado más medicación de rescate (63%) que corticosteroides inhalados (23%) en las últimas 4

semanas[44]. Esto puede ser consecuencia de una sobreestimación del control del asma, que no encaja con la gravedad de los síntomas.

Poniendo en conjunto los dos primeros trabajos de esta tesis, se objetiva que entre un 40 y un 50% de los pacientes no estaban recibiendo tratamiento con corticosteroides inhalados ni de forma pautada ni a demanda y que en muchos de ellos el tratamiento principal eran los SABA a demanda. Una cifra similar a la observada en el estudio ASMAB II, donde sólo un 31% de los pacientes que acudían a Urgencias utilizaban de forma regular corticosteroides inhalados[36].

Es conocido que la excesiva dependencia de SABA a expensas de la terapia de control con corticosteroides inhalados está asociada con un incremento de la mortalidad, como resultado de un tratamiento insuficiente de la inflamación[45] y que los episodios de sobreuso de tratamiento de rescate son también predictivos de un incremento en el riesgo de exacerbaciones[46].

Al igual que ocurre en el resto de enfermedades crónicas, la mala adherencia al tratamiento regular de mantenimiento es una realidad también en el asma. Como estrategia para combatir este problema, las nuevas publicaciones avalan la terapia de mantenimiento y rescate anti-inflamatorio como tratamiento de elección en pacientes con asma moderada y grave, es decir, el uso de un inhalador único que contenga una combinación de broncodilatador y corticosteroide inhalado[47]. Incluso algunas guías como la GINA o la BTS (British Thoracic Society) ya proponen la introducción de los corticosteroides inhalados desde estadios iniciales de la enfermedad ya que hay estudios en los que se objetiva que esto produce un efecto beneficioso en la evolución de la enfermedad[48].

La causa más frecuentemente encontrada como desencadenante de las exacerbaciones (en más de la mitad de los casos) es la infección respiratoria, al igual que en estudios previos[649]. Hay evidencia de que la patología infecciosa respiratoria aguda incrementa al doble la probabilidad de sufrir una exacerbación de asma[50].

A pesar de ello, en nuestro caso un importante número de episodios se producen en los meses de mayo y junio, lo que habla del posible papel de la patología alergológica estacional.

Bien es cierto que la limitación más importante de este estudio es la imposibilidad del acceso a ciertos datos que no aparecen en las historias clínicas, debido al carácter retrospectivo del mismo. Aunque por otro lado, nuestra muestra es representativa de la práctica clínica en la vida real en nuestra área geográfica, y aporta una visión global al haberse recogido los datos en un mismo hospital, por un mismo equipo médico, a lo largo de un año natural completo, lo cual podría indicar que en realidad, sí existe un importante número de pacientes asmáticos que no estarían correctamente diagnosticados o que estarían recibiendo un tratamiento subóptimo y por lo tanto estarían mal controlados.

En ambos trabajo se objetiva un alto porcentaje de asmáticos infradiagnosticados y mal controlados, ya que más de un 40% de los pacientes que habían sufrido una exacerbación en el año previo no tenían un diagnóstico previo de asma, o no estaba registrado en la historia clínica de Urgencias.

Estas cifras del mal control del asma se corresponden con los resultados publicados en los últimos años de la encuesta REALISE[51], realizada en 8000 pacientes adultos con asma procedentes de 11 países europeos, donde más del 50% de los pacientes asmáticos no

estaban bien controlados, y en concreto en España el 52,3% no estaban controlados, el 34,2% parcialmente controlados y únicamente el 13,6% estaban bien controlados.

El control del asma con frecuencia se ve afectado por factores ajenos a la enfermedad, tal y como pueden ser la edad avanzada o la aparición concomitante de otras enfermedades como la enfermedad pulmonar obstructiva crónica (EPOC). Está demostrado que la función pulmonar de los pacientes asmáticos empeora a medida que aumenta su edad, al igual que aumenta el riesgo de hospitalización y muerte[52]. Por otro lado, autores como Postma y Rabe[53] y Lange et al[54] describen que los pacientes con síndrome de solapamiento asma-EPOC sufren un descenso más rápido del FEV_1, mayor frecuencia de síntomas respiratorios y de infecciones respiratorias, necesitan un tratamiento más intensivo, tienen mayor riesgo de hospitalización y mayores tasas de mortalidad que los pacientes con asma o EPOC aislados.

La prevalencia previamente descrita del síndrome de solapamiento asma-EPOC está entre un 13% y un 30%, en nuestra muestra aparece un 13,7%, y se asocia, al igual que la edad avanzada, con un peor control del asma, por un aumento del número de exacerbaciones y mayor probabilidad de recaídas.

Existen otras comorbilidades que también se asocian con un peor control del asma y con un aumento de exacerbaciones, como la hipertensión arterial, la diabetes mellitus y las patologías psiquiátricas, resultados similares a los descritos por Denlinger et al[55].

Otro aspecto a tener en cuenta es que algunos pacientes, acuden repetidamente a Urgencias tras una exacerbación, ya que bien por infratratamiento en el momento agudo o por mal control basal, presentan una reagudización de los síntomas tras una primera intervención en el centro hospitalario. Estas recaídas son una complicación

frecuente de las exacerbaciones de asma, en nuestros estudios un 6% de los pacientes sufrieron al menos una recaída en los primeros 15 días, cifras ligeramente inferiores a otras descritas previamente de un 15 o un 17%[56]. Esto podría deberse a que el tratamiento administrado en nuestro servicio de urgencias en la primera crisis sea más intensivo que en otros centros o también puede verse influenciado por la localización del hospital, ya que se encuentra situado en la periferia de la ciudad, por lo que es posible que ante una recaída de igual o menor gravedad, los pacientes acudieran al centro de salud de su área.

Con respecto a la eosinofilia y su asociación con determinados factores, la mayoría de estudios recientes han relacionado un aumento de los eosinófilos en sangre con un aumento en el número de exacerbaciones de asma y con una mayor probabilidad de ingreso hospitalario[57,58]. Sin embargo, en nuestros trabajos no encontramos asociación entre ésta y el número de exacerbaciones, ni tampoco con una mayor probabilidad de ingreso, resultados similares a los que describen Tran et al[59]. En nuestro caso podría ser consecuencia de que se objetiva una elevada frecuencia de la patología infecciosa como causa de las exacerbaciones, sin embargo la sospecha de una causa alérgica es claramente inferior, y con menores tasas de ingreso. Esto puede haber influenciado los recuentos de eosinófilos ya que en las crisis agudas de asma asociadas con infecciones virales del tracto respiratorio se ha demostrado un claro predominio de la inflamación neutrofílica[60].

Por el contrario, la eosinofilia sí que se asoció de manera significativa con una mayor probabilidad de recaída en nuestro estudio; el 32% de los pacientes que tuvieron

recaídas presentaban un recuento de eosinófilos en sangre mayor o igual a 400 eosinófilos/mm3, resultados similares a los publicados por Denlinger et al[55].

El seguimiento del paciente y las intervenciones posteriores de los especialistas tras una visita a Urgencias se han descrito como un factor importante a la hora de la prevención de nuevos episodios de reagudización[61]. En nuestro estudio únicamente un 15% de los pacientes fueron derivados un especialista en asma al ser dados de alta, cifra similar a la descrita por Hasegawa et al[62], lo que puede hacer a esta población más susceptible frente a nuevas exacerbaciones. Por ello es importante integrar a los especialistas en un mismo sistema para conseguir un ajuste óptimo del tratamiento tras la exacerbación de asma y así poder reducir la morbilidad de la enfermedad[63].

Como conclusiones de los primeros dos capítulos de esta tesis se extraen que la edad avanzada, la ausencia de un diagnóstico previo de asma, la enfermedad no controlada y la EPOC concomitante son características frecuentes entre los pacientes con exacerbaciones. Estos factores se asociaron a un mayor riesgo de ingreso hospitalario, así como las infecciones respiratorias, la gravedad de la exacerbación y la necesidad de tratamiento intensivo en urgencias. Hay un subgrupo de pacientes que tienen un mayor riesgo de recaída, principalmente los que tienen un asma no controlada y acuden varias veces a Urgencias a lo largo del año. El aumento de eosinófilos en sangre también conlleva un mayor riesgo de recaída y debe considerarse un marcador específico del fenotipo del asma, pero no un predictor de ingreso hospitalario.

La incidencia de exacerbaciones en pacientes con asma y bronquiectasias es alta, de hecho los asmáticos con bronquiectasias tienen de 1,6 a 2,6 más probabilidades de tener una exacerbación que los asmáticos que no las tienen[35]. Tal es así que, la coexistencia

de asma y bronquiectasias se ha asociado con un riesgo aumentado de exacerbación, hospitalización y fallo respiratorio crónico[34], además de hipersensibilidad frente a AINEs, enfermedad por reflujo gastroesofágico e incremento del número de eosinófilos en sangre periférica.

La prevalencia de bronquiectasias en pacientes con cualquier gravedad de asma es generalmente baja, si bien es cierto que su presencia varía en los diferentes estudios publicados, oscilando entre un 17,5% y un 80% de los casos de asma[64,65], aunque aumenta de forma considerable en pacientes con asma grave[30].

En nuestro tercer trabajo, que estudia la asociación entre asma moderada-grave y bronquiectasias, se objetiva que las bronquiectasias afectan a casi la mitad de los pacientes (objetivadas con TC torácica de alta resolución) y son más frecuentes en asma de mayor gravedad, al igual que lo descrito en estudios previos[32].

Además, objetivamos una asociación estadísticamente significativa entre la presencia de bronquiectasias y unos niveles más altos de eosinófilos en sangre, que podría hablar de una relación de las mismas con el asma alérgica. Si bien es cierto que todavía no se ha establecido con precisión una relación etiológica clara y sigue existiendo la incógnita de si las bronquiectasias son causa o consecuencia del asma. Es difícil determinar si la gravedad del asma en sujetos con bronquiectasias coexistentes se debe a la presencia de bronquiectasias o si la presencia de bronquiectasias es una manifestación de la gravedad del asma.

La prevalencia de asma en pacientes con bronquiectasias está entre un 2,7% y un 40%[66]. En el Spanish Registry Study (2047 pacientes) se identificó el asma como la etiología de

las bronquiectasias en un 5,4% de los pacientes y se correlacionó con una peor función pulmonar pero con un menor número de infecciones respiratorias[67].

Se ha descrito que en pacientes con asma moderada y grave, el tratamiento regular con macrólidos supone un descenso de la tasa de exacerbaciones graves que requieren tratamiento con corticosteroides sistémicos u hospitalización[68]. En nuestro trabajo únicamente había 3 pacientes en tratamiento de mantenimiento con azitromicina, por lo que no fue posible realizar un análisis de los mismos con resultados concluyentes, pero los hallazgos previos sugieren que el añadir este fármaco a los regímenes de tratamiento regulares podría resultar beneficioso para esta población.

Por lo tanto, a modo de resumen, en nuestro último trabajo se identifican bronquiectasias en aproximadamente la mitad de los sujetos con asma moderada-severa y éstas se asocian con un riesgo aumentado de hospitalización y con niveles más altos de eosinófilos en sangre. Los datos también sugieren una asociación entre las bronquiectasias y la hipersensibilidad frente a AINEs o la enfermedad por reflujo gastroesofágico, al igual que en algunos trabajos previos[55,69], aunque estos hallazgos requieren un mayor estudio ya que hay poca información y muchos de los trabajos que existen tienen limitaciones y resultados muy dispares.

CONCLUSIONES

1. El asma es un síndrome complejo que se caracteriza por su gran variabilidad a lo largo del curso de la enfermedad. A pesar de las mejoras en el diagnóstico y en el tratamiento en los últimos años y del descenso de las tasas de mortalidad, las exacerbaciones continúan apareciendo y son la principal causa de morbilidad y mortalidad en asma.

2. Existen ciertos factores tales como la edad avanzada, el mal control del asma, la presencia de bronquiectasias o la EPOC concomitante que se asocian a un riesgo aumentado de ingreso hospitalario y que se deberían de tener en cuenta a la hora del manejo y tratamiento de los pacientes con alguna de estas características.

3. Existe un porcentaje de pacientes asmáticos que presentan un mayor riesgo de recaída tras una exacerbación, principalmente los que tienen mayores niveles de eosinófilos en sangre, un asma no controlada o acuden varias veces a Urgencias a lo largo del año. En ellos sería apropiado realizar un seguimiento estrecho tras cada una de las reagudizaciones.

4. Según lo obtenido en nuestros datos, la eosinofilia periférica se asocia con un mayor riesgo de recaída y con la presencia de bronquiectasias, aunque no con un aumento del riesgo de ingreso hospitalario; podría considerarse la misma como un marcador específico del fenotipo del asma.

5. En pacientes con asma moderada o grave es importante detectar la presencia de bronquiectasias ya que implican un fenotipo determinado de paciente con una mayor gravedad de la enfermedad y la concomitancia de ciertas comorbilidades.

6. Por último, consideramos que conocer los factores de riesgo de las exacerbaciones y los indicadores potenciales de gravedad, establecer un tratamiento adecuado y unas medidas preventivas eficaces ayudaran a conseguir nuestro objetivo principal: una mejoría del control actual del asma y una disminución del riesgo futuro.

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Facultad de Medicina

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TESIS DOCTORAL

EXACERBACIONES DE ASMA

EN EL SERVICIO DE URGENCIAS DEL HOSPITAL UNIVERSITARIO LA PAZ

Memoria presentada por **Beatriz Pola Bibián** para acceder al grado de Doctor en la Facultad de Medicina de la Universidad Autónoma de Madrid

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Resumen tesis doctoral "EXACERBACIONES DE ASMA EN EL SERVICIO DE URGENCIAS DEL HOSPITAL UNIVERSITARIO LA PAZ".

La presente tesis se presenta como un compendio de publicaciones científicas de las que la candidata a Doctora es primera autora de dos de ellas y segunda autora de la tercera.

En España apenas se conocen datos sobre el perfil de los pacientes asmáticos que sufren exacerbaciones. En 2009 se publicó un estudio realizado en Barcelona incluyendo 262 episodios de exacerbación asmática, atendidas en hospitales o en visita domiciliaria, durante 2 meses. Previamente, existen datos retrospectivos analizando algunas variables en el área de la calidad asistencial o la epidemiología . Sin embargo, todavía son muchos los aspectos que se desconocen y que podrían servir para prevenir la aparición de exacerbaciones asmáticas.

El objetivo principal de esta tesis es estudiar las características clínicas y demográficas de los pacientes asmáticos de 14 años en adelante, atendidos en el Servicio de Urgencias del Hospital Universitario La Paz, por una exacerbación asmática de cualquier nivel de gravedad, a lo largo del periodo natural del año 2014. Como objetivo secundario se postula, entre otros, la determinación de la prevalencia de bronquiectasias en pacientes con asma moderada-grave, que sufren frecuentes exacerbaciones, con el fin de caracterizarlos mejor tanto epidemiológica como clínicamente.

En primer lugar, se llevó a cabo un estudio epidemiológico, abierto, observacional retrospectivo (no intervencionista) en el que se incluyeron todos los pacientes mayores de 14 años, que desde el 1 de enero de 2014 al 31 de diciembre de 2014, fueron atendidos en el Servicio de Urgencias del Hospital Universitario La Paz, con clínica sugerente de exacerbación asmática.

En el primer trabajo la población de estudio comprendió 831 pacientes (888 eventos de exacerbación). Los factores de riesgo de hospitalización fueron: edad avanzada, la ausencia de un diagnóstico previo de asma, el asma mal controlada, la infección

respiratoria y la exacerbación grave con mayor necesidad de tratamiento. La tasa de hospitalización fue significativamente menor en pacientes con ≥400 eosinófilos/mm3.

En el segundo trabajo se analizaron 52 pacientes (de los 831 previos), que sufrieron una recaída después de haber sido atendidos en el Servicio de Urgencias, haciendo un total de 66 episodios. La probabilidad promedio de recaída fue de 6 ± 0,8%. Los factores relacionados con una mayor probabilidad de recaída fueron: haber tenido visitas múltiples al Servicio de Urgencias en un año, asma no controlada, sibilancias en la auscultación pulmonar, eosinofilia periférica ≥400/mm3 y haber sido dado de alta en la primera visita al Servicio de Urgencias.

En segundo lugar, se realizó un estudio epidemiológico también abierto, observacional retrospectivo sobre el que versa el tercer capítulo de esta tesis. En él se analizaron las historias clínicas de 264 pacientes derivados a la Consulta de Asma Grave del Hospital La Paz, entre los años 2010 y 2013, con sospecha de asma grave o de control difícil.

Se identificaron bronquiectasias en 86 pacientes. Estos pacientes tenían hipersensibilidad a antiinflamatorios no esteroideos y enfermedad por reflujo gastroesofágico con mayor frecuencia que los sujetos sin bronquiectasias, pero menor frecuencia de dermatitis atópica. Los sujetos con bronquiectasias tuvieron una tasa mayor de hospitalización por exacerbaciones de asma y niveles más altos de eosinófilos en sangre que los sujetos sin bronquiectasias.